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INTERNAL MEDICINE

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II. Medical Aspects of Delayed Convalescence
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III. Psychologic Aspects of Delayed Convalescence
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An Outline of the Use of Iodine in Endemic Goiter
Henry N. Wagner Jr.

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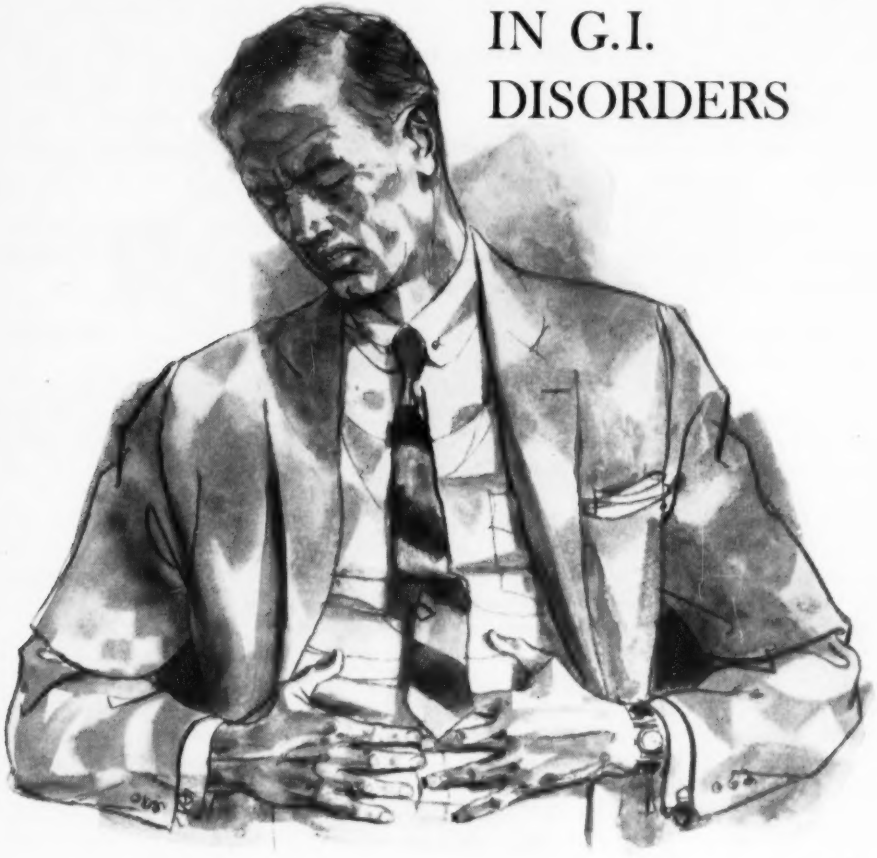

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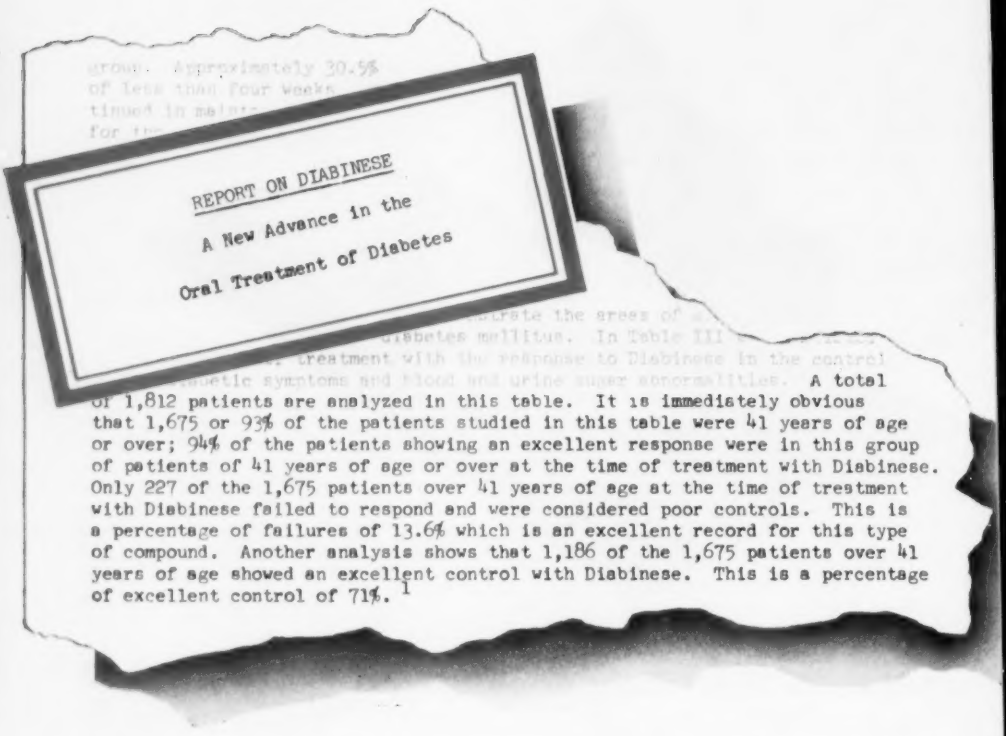
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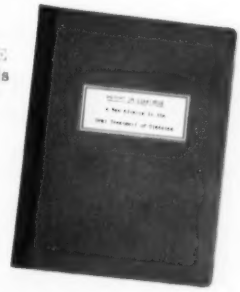

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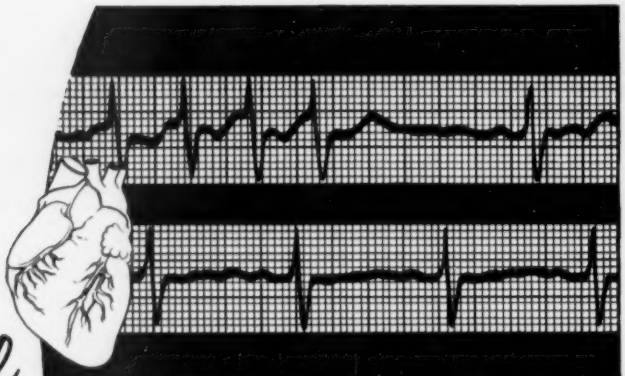

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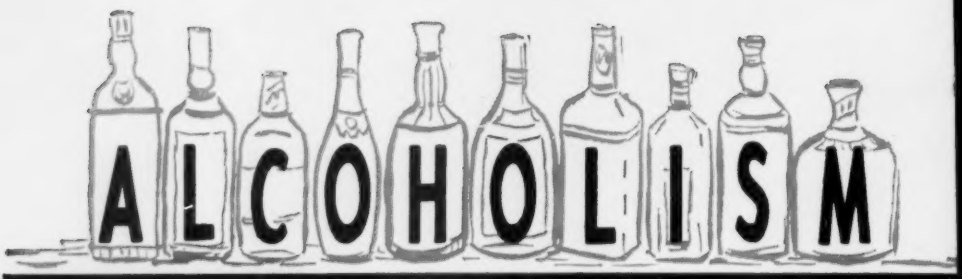

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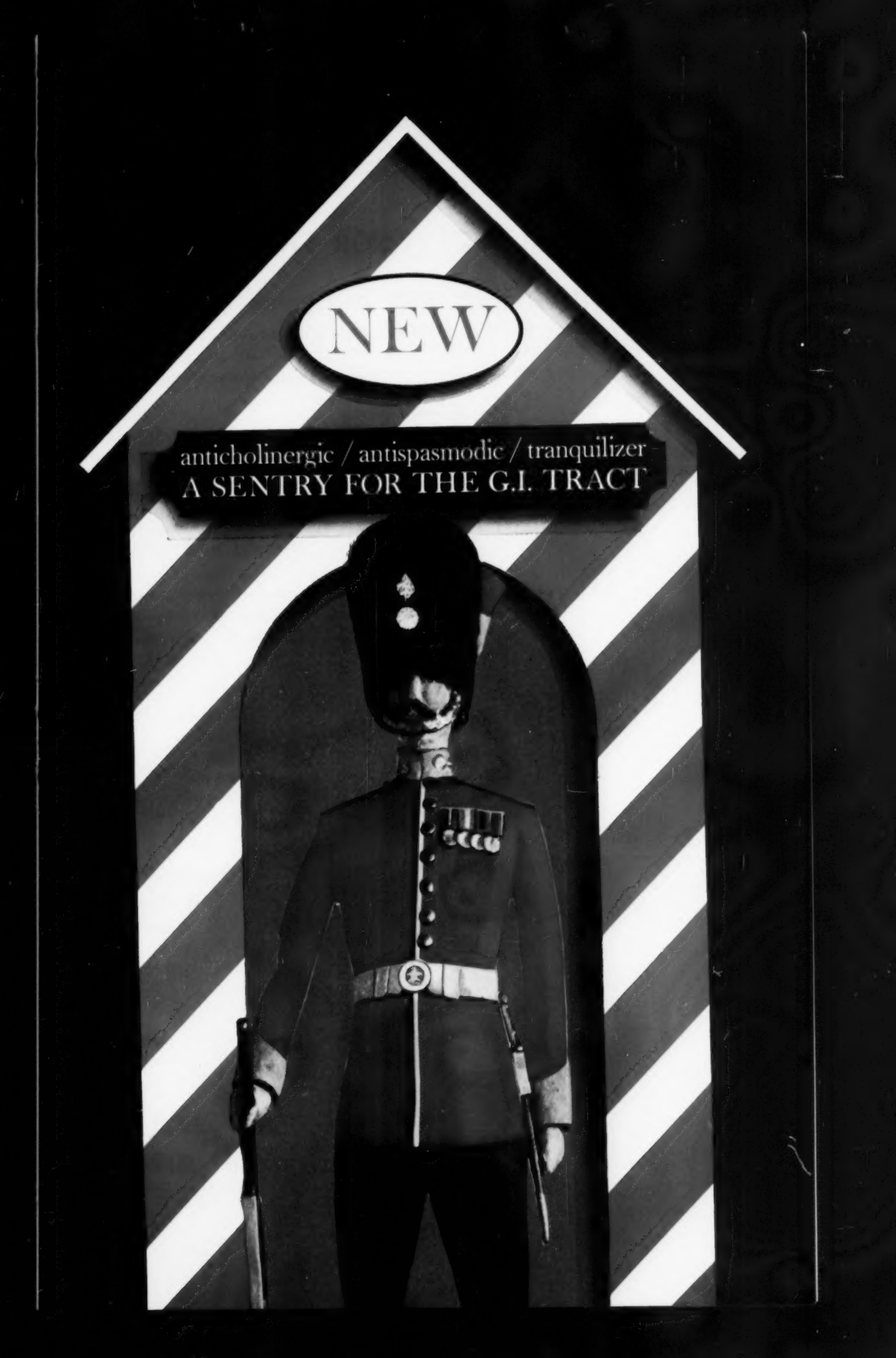
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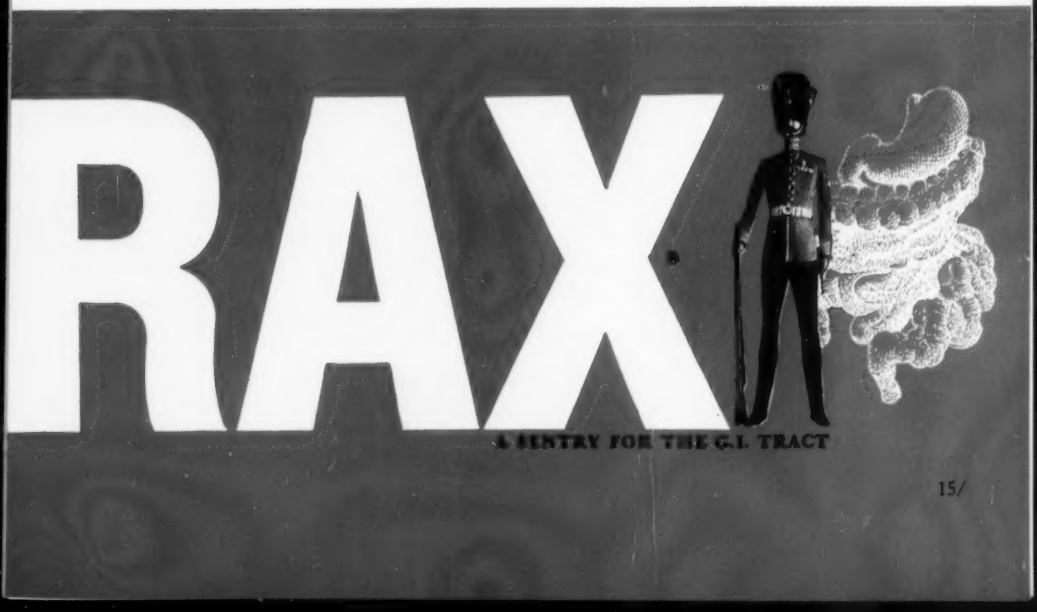

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Long-Term Treatment of Bronchiectasis and Chronic Bronchitis

A Controlled Study of the Effects of Tetracycline, Penicillin, and an Oleandomycin-Penicillin Mixture

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Several antibiotics are effective in the treatment of acute bacterial infections of the lower respiratory tract in patients with chronic bronchitis and bronchiectasis. However, studies designed to test the effectiveness of antibiotics in treating the low-grade, continuing infection in patients with these diseases and in preventing acute infections of the lower respiratory tract in these patients have had contradictory results.

Penicillin was used extensively both systemically and by aerosol in the years immediately following its introduction. Comprehensive reports have been made by Barach and his associates [1] and by Finke.[2] Penicillin was never successful in eradicating Hemophilus influenzae, which Mulder and his associates [3] and others [4,5] believe to be the most important pathogenic agent in bronchiectasis and chronic bronchitis, and in recent years the increasing prevalence of penicillin-resistant staphylococci have further limited the effectiveness of penicillin.

Mulder and his associates [3] reported excellent results in chronic bronchitis when penicillin and streptomycin were given intramuscularly, although Knox and his associates [6] were not able to eliminate H. influenzae from the sputum or to decrease exacerbations of chronic bronchitis with aerosolized penicillin and streptomycin.

Franklin and Garrod [7] administered chloramphenicol to 36 patients with bronchiectasis in doses of 20 mg. per kilogram three times a day. These doses consistently diminished the volume of sputum and eliminated pathogenic bacteria. However, this investigation was discontinued when one patient died of aplastic anemia.

The tetracyclines have been administered for varying periods of time to small groups of patients by several investigators.[1,2,8] A few controlled studies on the effectiveness of these antibiotics have been reported. McVay and Sprunt [9] were able to prevent an appreciable number of acute exacerbations in 21 patients with bronchiectasis and chronic bronchitis by the oral administration of 500 mg. of chlortetracycline a day. Increases in leukocytes and hematocrit were observed and sedimentation rates were consistently lower in the antibiotic-treated pa-

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tients than in a similar group of patients who received placebos. On the other hand, Lepper and Pearson [10] did not observe any difference between patients who received a similar dose of tetracycline and placebo-treated control patients. Allibone and associates [11] reported the disappearance of H. influenzae from the sputum of all patients with bronchiectasis who were treated with a combination of sulfonamides and tetracycline or erythromycin, although these organisms did not disappear when either antibiotic was used alone.

Fox and associates [12] demonstrated that when tetracycline was administered intravenously to patients with chronic bronchitis and bronchiectasis in doses of 1 to 1.5 gm. per day the volume and purulence of the sputum were reduced. This therapy eliminated most of the potentially pathogenic organisms from the sputum and apparently improved pulmonary function in patients with chronic bronchitis.

The present study was begun in a large group of patients to evaluate the effect over long periods of time of orally administered antibiotics, tetracycline, penicillin, and an oleandomycin-penicillin combination in controlling the pulmonary infections that may occur in these diseases. The results were evaluated not only by clinical criteria but also by frequent bacteriological examinations of the sputum, tests of pulmonary function, and serum proteins. The results of pretreatment serum protein studies and pulmonary function tests have been previously reported.[13,14] The present report deals with the effects of antibiotic therapy in 67 patients. Patients were studied from 3 to 18 months. Only patients treated three or more months are included in this report.

Methods

Patients were included in this study if (1) bronchography revealed one or more areas of bronchiectasis and/or (2) they had had a history of chronic productive cough for one or more years and repeated lower respiratory tract infections without another reason for the cough and sputum.

Patients in whom no area of bronchiectasis could be demonstrated by bronchography were diagnosed as having chronic bronchitis. In the few cases in which bronchography could not be performed, the diagnosis of the respiratory illness was listed as undetermined.

As patients entered the study they were assigned in rotation to one of four treatment groups. Occasionally a patient was placed out of the strict order of rotation in order to make the groups more nearly uniform with respect to sex, age, and certain complications, such as hypogammaglobulinemia. All placements were made by one of us who had not examined the patients beforehand and who did not make bacteriologic examinations of the sputum or tests of pulmonary function and did not participate in the evaluation of the clinical status of patients when they returned to the clinic.

All of the other participants in the investigation and all of the patients were unaware of what drug the patient was receiving. Table 1 shows that the groups were very comparable.

One group of patients received 2 gm. of tetracycline daily in four divided doses one-half hour before each meal and at bedtime. During the first year of the study tetracycline hydrochloride was used, while in the second year tetracycline hydrochloride with citrate buffer was substituted. A second group received 1 gm. of potassium penicillin G a day (1,600,000 units) in four divided doses; the third group received 2 gm. of

TABLE 1.—*Characteristics of Treatment Groups*

Treatment Group	Patients, No.	Mean Age	Above 40 Yr., No.	M. B. C. <50% Predicted Normal, No.*	Illness Lasting >10 Yr., No.	Diagnosis		
						Bronchiectasis	Bronchitis	Undetermined
Placebo	17	43.5	8	8	11	9	5	3
Tetracycline	17	47.4	11	10	10	14	2	1
Oleandomycin-penicillin	16	47.4	10	5	8	11	3	2
Penicillin	17	47.8	12	6	9	11	4	2

* Maximum breathing capacity.

a combination of oleandomycin and penicillin (1.3 gm. of oleandomycin-penicillin and 0.7 gm. of penicillin) a day in four divided doses. The fourth group received a sucrose placebo four times a day. All medications were dispensed in capsules of identical shape, size, and color.* Every patient was started on eight of these capsules each day. If an acute respiratory illness required antibiotic therapy, the usual therapy was discontinued and the patient was given the therapeutic regimen that appeared to be indicated, either as an outpatient or after hospitalization. The physician in charge of the patient during this illness was not informed as to which antibiotic the patient had been receiving. At the termination of the episode the patient was returned to his original treatment group.

Patients who discontinued therapy have been included in the tabulations up to the point where therapy was stopped. No patient has been excluded who remained on therapy for at least three months. One patient who was treated for four months with oleandomycin-penicillin withdrew from therapy and was lost from observation. Only the four months of therapy are included in this report.

Prior to the initiation of therapy chest x-rays were taken, a complete blood cell count was done, and the serum total proteins, the protein electrophorectic patterns, and the C-reactive protein determined on one or more occasions. One patient in each group had hypogammaglobulinemia confirmed by repeated electrophorectic patterns on paper strips.

One or more sputum samples were collected and treated in the following manner. Sputum was homogenized in sterile isotonic sodium chloride solution and cultures made. A fleck from the sputum homogenate was washed three times in isotonic saline, and cultures made also from this. Both samples were cultured on the following media: human blood agar, penicillin blood agar (1 unit of penicillin per milliliter), eosin-methylene-blue agar, and Sabouraud's agar. All blood media were inoculated with a streak of Staphylococcus to aid in the isolation of H. influenzae. Duplicate cultures were made on all media except Sabouraud's; one set was incubated aerobically and one under CO_2 tension. Sabouraud cultures were incubated aerobically. Organisms were identified by standard bacteriologic methods, and the relative numbers of each organism isolated were recorded. When possible Diplococcus pneumoniae (pneumococci) and β-streptococci were grouped with the sera available. Coagulase tests were done on staphylococci, and coagulase-positive staphylococci were bacteriophage-typed, tested for the production of α-hemolysin, and tested for sensitivity to penicillin, erythromycin, tetracycline, and oleandomycin. H. influenzae organisms were also tested for sensitivity to the above four antibiotics. The cultures were saved by weekly transfers in Levinthal medium. When the patient was not able to produce sputum, nose and throat swabs were taken and cultured in a similar manner.

The following tests of pulmonary function were done prior to therapy: vital capacity, one-second vital capacity, maximum breathing capacity, index of alveolar mixing, diffusing capacity for oxygen, and venous admixture. These tests were repeated one year later. The pretreatment and one-year post-treatment results of the first four of these tests are presented in this paper. Methods used in performing these tests have been previously described.[14]

After therapy was begun the patients were seen at monthly intervals. At each visit a blood sample was taken and sputum collected. A history was obtained with particular attention to respiratory illnesses and possible side-effects of the drug used, and the patient was weighed and examined. Patients' estimates of their daily sputum volume given at each visit were checked against 24-hour collections for several months during the course of this study.

A patient was considered to have had a respiratory tract illness when he gave a history of an illness with symptoms predominately involving the respiratory tract in which there was either an acute exacerbation of previous symptoms or the appearance of new symptoms. When a patient complained of the acute appearance of dyspnea without other respiratory symptoms this was not considered to be a respiratory tract illness. Respiratory illnesses were classified as affecting the lower respiratory tract if the illness was associated with an increase in cough and sputum.

During the first year of this study an illness was classified as febrile when the patient reported fever. Since it was discovered that all patients did not have thermometers, in the second half of the study thermometers were distributed to the patients and they were instructed in their use. During this part of the study a patient was considered to have fever if his oral temperature exceeded 100 F one or more times in a day. There was no appreciable change in the incidence of fever in any of the treatment groups after thermometers had been distributed. All statistical comparisons were made by "Student's" t-test. The average value for each person during the period of observation was used. From these values group means were determined for each treatment group for each of the functions considered. Within the groups there was much individual variation

* The Chas. Pfizer & Company, Inc., Brooklyn, and the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y., provided the antibiotics and placebos used in this study.

TABLE 2.—*Mean Rates of Acute Respiratory Illness Following Therapy* *

	Treatment Group †							
	Placebo		Tetracycline		Oleandomycin-Penicillin		Penicillin	
	Mean No.	S. E.	Mean No.	S. E.	Mean No.	S. E.	Mean No.	S. E.
Episodes of upper respiratory illness	4.20	±0.8	2.88	±0.4	2.52	±0.6	3.00	±0.7
Episodes of lower respiratory illness	3.36	±0.6	1.32	±0.3	1.92	±0.3	2.28	±0.4
Episodes of lower respiratory illness with fever	1.44	±0.3	0.12	±0.1	0.72	±0.3	1.56	±0.5
Days of lower respiratory illness	29.2	±5.1	14.5	±2.9	14.5	±2.8	21.8	±7.3
Days of lower respiratory illness with fever	4.44	±1.3	0.84	±0.6	2.64	±0.9	11.64	±3.5

		t	*P*
Episodes of lower respiratory illness	Tetracycline versus placebo	3.4	<0.01
Episodes of lower respiratory illness with fever	Tetracycline versus placebo	3.7	<0.001
	Tetracycline versus penicillin	3.0	<0.01
Days of lower respiratory illness	Tetracycline versus placebo	2.8	<0.01
	Oleandomycin-penicillin versus placebo	2.4	<0.05
Days of lower respiratory illness with fever	Tetracycline versus placebo	2.2	<0.05
	Tetracycline versus penicillin	3.1	<0.01
	Oleandomycin-penicillin versus penicillin	2.3	<0.05

All other differences not statistically significant.

* Illnesses/patient/yr.
† S. E. indicates standard error.

in all of the measures. In the presentation of results, group means and their standard errors have been given.

Results

1. *Acute Respiratory Illnesses Following Therapy.*—It will be seen from Table 2 that the patients treated with tetracycline had fewer illnesses in both the upper and lower respiratory tract than patients in any of the other groups but that only the differences between the tetracycline and the placebo groups and the tetracycline and the penicillin groups with respect to infections of the lower respiratory tract were statistically significant.

The results obtained with the oleandomycin-penicillin mixture appeared to be more favorable for both upper and lower respiratory tract illnesses than treatment with penicillin or placebo. However, the differences were statistically significant only between the oleandomycin-penicillin and placebo groups with respect to days of lower respiratory illness and between the oleandomycin-penicillin and the penicillin groups with respect to days of lower respiratory illnesses with fever.

There was one patient with hypogammaglobulinemia in each group. When these patients were eliminated in the statistical evaluation, all results that were previously significant remained so. When only the patients with bronchiectasis or patients more than 40 years of age or those with maximum breathing capacities less than 50% of the predicted values were considered, results, between placebo and treated groups were not statistically significant. When those patients whose illness had lasted 10 or more years were tabulated separately there were significantly fewer days of fever with lower respiratory infection in the tetracycline treated group than in the placebo group ($t=2.4$, $p<0.05$). Days of lower respiratory infection, however, were not significantly different in these two groups. Tetracycline-treated patients over 40 years of age and

patients in the same age group treated with oleandomycin-penicillin had fewer days of fever than patients in this same age group who were treated with penicillin ($t=2.2$, $p<0.05$, and $t=2.2$, $p<0.05$, respectively).

2. *Weight Gain and Volume and Color of Sputum.*—There was no mean weight gain in the placebo group, while there was a gain in weight of 3 lb. in the patients treated with tetracycline and oleandomycin-penicillin and a 1 lb. weight gain in those treated with penicillin alone. Daily sputum volume fell in every group: from 128 cc. to 82 cc. in the placebo group, from 74 cc. to 49 cc. in the tetracycline group, from 64 cc. to 51 cc. in the oleandomycin-penicillin treated group, and from 93 cc. to 44 cc. in the group treated with penicillin alone.

Only in the placebo group did the sputum of more patients change from white to purulent than from purulent to white. However, none of the above-mentioned differences were statistically significant.

3. *Deaths, Hospitalizations, Additional Treatment Required, and Days of Confinement to Bed.*—As shown in Table 3, patients receiving placebos required more hospitalizations and more courses of antibiotic treatment for illnesses of the respiratory tract than patients in any of the antibiotic-treated groups. Tetracycline-treated patients did not require any hospitalizations during the period of observation covered in this report, and only one patient treated with tetracycline required additional antibiotic treatment. Patients in the tetracycline group were likewise confined to bed less frequently than patients in any of the other groups. None of these differences, however, were statistically significant.

TABLE 3.—*Additional Treatment Required, Days Confined to Bed, and Hospitalization in Four Treatment Groups*

	Treatment Group			
	Placebo	Tetracycline	Oleandomycin-Penicillin	Penicillin
Times additional antibiotic treatment required for respiratory infections	7	0	2	3
Days confined to bed because of respiratory infections	47	38	45	98
Hospitalizations required for respiratory infections	7	1	1	4

Five deaths occurred during the period of observation, all among antibiotic-treated patients. One patient died from pulmonary hemorrhage in the tetracycline-treated group. One patient in the group treated with oleandomycin-penicillin died of bronchopneumonia and respiratory insufficiency. Necropsy showed Hamman-Rich disease. He had not had a bronchogram, and at autopsy no evidence of bronchiectasis was found. Rates of illness for this patient were lower than the average for patients treated with oleandomycin-penicillin. Three patients died in the group treated with penicillin. One patient with portal cirrhosis died in hepatic coma, and a second developed bronchopneumonia and died shortly after admission to the hospital. A third patient, who had hypogammaglobulinemia, developed a bronchopleural fistula and empyema after resection of the right middle lobe and a basilar segment of the right lower lobe and died with Pseudomonas bacteremia.

4. *Bacteriological Findings.*—The percentages of nose, throat, and sputum cultures from each patient from which H. influenzae, D. pneumoniae, coagulase-positive staphylococci and yeasts were grown before and after treatment were calculated. Mean rates of isolation for each group of patients are shown in Table 4. The rates of isolation of H. influenzae fell after treatment only among the patients treated with tetracycline, although this decrease was not statistically significant.

There was a significant fall in the mean rate of isolation of pneumococci in the tetracycline-treated patients ($t=2.4$, $p<0.05$), whereas an increase in the mean rate of isolation of pneumococci occurred in the placebo group ($t=3.5$, $p<0.01$). Treatment with tetracycline or the oleandomycin-penicillin combination also caused a

TABLE 4.—*Positive Bacteriologic Cultures Before and After Treatment*

Micro-Organism	Relation to Therapy	Treatment Group: Placebo	Tetracycline	Oleandomycin-Penicillin	Penicillin
		Cultures Before Treatment, No.			
	Before	49	52	44	47
	After	149	144	123	153
		Mean Rate of Positive Isolations, %			
H. influenzae	Before	30±8*	26±8.2	17±7.2	28±5.8
	After	29±7	12±4.1	24±7.5	37±9.6
D. pneumoniae	Before	0	25±6.3	14±6	14±4.4
	After	14±5.3	3±0.5	2±2	5±3.9
Coag.-positive staphylococci	Before	16±5.5	15±4.4	19±6.2	15±6.6
	After	6±4.9	3±1.5	3±2	6±1.5
Yeast	Before	45±5.9	20±6.5	13±8	23±8.5
	After	29±7.1	12±6.5	19±6.2	29±6.4

* Standard error.

significant decrease in the mean rate of isolation of coagulase-positive staphylococci ($t=2.2$, $p<0.05$ in both cases). The decrease in the other two treatment groups was not statistically significant. The rate of isolation of yeasts did not increase significantly with antibiotic therapy.

To determine the importance of H. influenzae, D. pneumoniae, and coagulase-positive staphylococci in causing acute respiratory infection in patients with bronchiectasis and chronic bronchitis an analysis was made in which the patients were grouped according to whether one or another of these species was isolated after treatment. Results are given in Table 5. Patients from whom H. influenzae was cultured one or more times after treatment had significantly more days of lower respiratory tract illness than those from whom H. influenzae had never been cultured ($t=2.2$, $p<0.05$). The other differences were not significant, but the mean rates of respiratory illness in patients from whom the other species of bacteria had been cultured were higher except that the recovery of D. pneumoniae did not increase the mean numbers of days of lower respiratory illness with fever.

5. *C-Reactive Protein.*—C-reactive protein determinations were graded from 0 to 6+. Although mean values for the group fell more in antibiotic-treated patients than in the placebo group, these differences were not statistically significant.

6. *Pulmonary-Function Tests.*—Results of studies of vital capacity, one-second vital capacity, maximum breathing capacity, and index of alveolar mixing, performed before treatment and repeated one year later, are seen in Table 6. Differences were not statistically significant, although there was some tendency for the index of alveolar mixing to improve in the patients treated with tetracycline and to become worse in patients who received placebos.

7. *Side-Effects of Therapy.*—Reactions to the drugs administered are summarized

TABLE 5.—*Rate of Respiratory Infection in Patients from Whom H. Influenzae, Coagulase-Positive Staphylococci, or D. Pneumoniae Were Cultured After Treatment*

Micro-organism	Cultured from Patient at Any Time	Pts., No.	Mean Days Lower Respiratory Illness, Patient/Yr., (%)*: All Illnesses, Mean No.	All Illnesses, S. E.	Febrile Illnesses, Mean No.	Febrile Illnesses, S. E.
H. influenzae	Yes	45	25.2	2.24	5.3	1.5
	No	22	13.2	3.4	3.6	1.7
Pneumococci	Yes	27	26.4	4.1	4.3	1.8
	No	40	18.0	3.4	4.3	1.4
Coagulase-positive staphylococci	Yes	37	21.6	3.9	7.2	2.4
	No	30	14.4	3.9	3.5	1.2

* S. E. indicates standard error.

TABLE 6.—*Mean Results of Pulmonary Function Tests on Each Treatment Group*

Treatment Group	Patients Tested, No.			Relation to Therapy	Vital Capacity, %	1 Sec. Vital Capacity, % *	Maximum Breathing Capacity, % †	Index of Alveolar Mixing, % ‡
	Bronchiectasis	Chronic Bronchitis	Diagnosis Undetermined					
Placebo	6	2	1	Before	71	61	62	2.6
				After §	71	61	54	5.0
Tetracycline	7	1	1	Before	57	55	45	5.3
				After	66	51	43	4.0
Oleandomycin-penicillin	7	0	1	Before	56	60	42	3.4
				After	61	57	49	4.1
Penicillin	8	0	0	Before	61	63	42	3 3
				After	70	53	45	3.7

* % of total vital capacity.
† % of predicted values.
‡ % of nitrogen in sample at the end of 7 min.
§ After 1 yr. of therapy.

in Table 7. Diarrhea occurred in at least one patient in each group. Persistent diarrhea occurred more frequently in the group treated with tetracycline than in other treatment groups. However, diarrhea was never serious in any case and subsided as soon as the dose of the drug was reduced.

Comment

The effectiveness of continuous therapy with antibiotics must be judged according to whether they prevented or ameliorated acute episodes of respiratory illness and whether they produced any improvement in the underlying disease or any slowing of its progress. The similarity of the treatment groups and the double-blind manner in which the observations were made in our study should have shown any definite effects of such treatment within the limitations of the numbers of patients and the duration of observation.

The accuracy of results obtained in part from histories of outpatients depends on the reliability of the patients themselves, and this is difficult to evaluate objectively. While the present study was still in progress the British Medical Research Council [15] reported on the effect of 2 gm. of oxytetracycline or penicillin twice weekly compared to placebos in 116 patients with bronchiectasis. The design of this study was similar to that of the present one, except that studies were not made of the flora of the sputum, the pulmonary function, or the serum proteins, and the results were likewise similar. This tends to increase the confidence with which results of the present study may be accepted.

TABLE 7.—*Untoward Reactions from Therapeutic Agents Used*

Treatment Group	Patients, No.	Patient-Mo. Treated	Patients with Any Therapy Reaction, No.	Cases of Diarrhea, No.	Cases of Abdominal Pain Without Diarrhea, No.	Moniliasis	Dizziness	Reduced Dose, No.*	Dose Reduced to Capsules/Day
Placebo	17	153	1	1	0	0	0	1	6
Tetracycline	17	171	4	3 †	1	1 ‡	0	4	4, 2, 4, & 6, respectively
Oleandomycin-penicillin	16	148	2	1	1	0	1	2	2 & 4, respectively
Penicillin	17	158	4	3 §	1	0	0	2	4 & 4, respectively

* Patients placed on reduced dose because of drug reactions.
† Diarrhea was bloody in 1 case.
‡ Vaginal moniliasis.
§ Temporary reduction of dose. Patients were able to take full dose later

From our observations it appears that tetracycline in the dose used was quite effective as a prophylactic agent in preventing acute lower respiratory infections. Although the daily dose was comparatively high and was given for long periods of time, side-effects, such as diarrhea, were not especially frequent or severe and were easily controllable. In addition, none of the patients on reduced doses of tetracycline had fever with any of their respiratory infections, nor was their rate of lower respiratory infection higher than that of the entire group.

Penicillin in the doses used by us was no more effective than placebo therapy.

Treatment with oleandomycin and penicillin in combination reduced the rate at which coagulase-positive staphylococci were isolated and diminished the number of days during which patients were ill with lower respiratory tract infections. However, it was not significantly better in any other respect than placebo therapy.

At this point in the study it is impossible to interpret the significance of the 10% case fatality rate among patients in the antibiotic-treatment groups as compared with the absence of deaths in the placebo group. The loss of these patients does not seem to account for the observed differences in respiratory illnesses among the groups. Nevertheless, at the present time the effect of the deaths is a decreased mean survival time among patients receiving continuous antibiotic prophylaxis, which, if it continues to be present as the study progresses, must be evaluated against the gain in the number of days during which the patients were free from lower respiratory infections.

Some of the patients were lost from the study after three months or more of observation. Although there was a tendency for patients with the least favorable effect to discontinue their clinic attendance, this was not the cause of significant differences among the groups. It did affect the rates of respiratory illness, and so the observation of two to four upper respiratory illnesses and one to three lower respiratory illnesses per year might not represent accurate mean rates for persons with bronchiectasis or bronchitis. The attrition of patients from the study also makes it difficult to evaluate the effectiveness of treatment in relation to duration of therapy. The continuation of patients with a favorable response might give a false appearance of continued effectiveness of treatment with an antibiotic. On preliminary analysis our data appear to indicate that the differences in the antibiotic and placebo groups were as great during the second winter as during the first. However, there was a period, generally agreeing with the summer months, in which respiratory illnesses were just as great in the tetracycline group as in the placebo group.

Although tetracycline was effective in reducing the frequency and duration of acute episodes, its efficacy in improving the chronic underlying disease in a period of one year has not been demonstrated. If, as many authors suggest,[3-5,11,16] H. influenzae, D. pneumoniae, and coagulase-positive staphylococci are important in causing progression of the pathologic processes of chronic bronchitis and bronchiectasis, any decrease in the progression of the disease from a reduction of these species produced by tetracycline in our patients must be a long-term difference.

None of the antibiotics administered to our patients altered sputum volume or purulence or caused significant weight gain. Pulmonary function was not appreciably improved by therapy, and C-reactive protein was not significantly decreased. It is obvious that a longer period of observation is needed before we can determine the effect of these antibiotics on the underlying bronchitis or bronchiectasis.

Summary

In a double-blind study, 67 patients with chronic bronchitis or bronchiectasis were placed in four comparable groups and treated orally with tetracycline, penicillin, a combination of oleandomycin and penicillin or a placebo for a period of 3 to 22 months.

Patients who received tetracycline had significantly fewer lower respiratory illnesses, febrile or afebrile, than patients treated with placebos. The average duration of these illnesses was shorter in patients treated with tetracycline. They also had significantly fewer days of respiratory illness with or without fever than patients treated with penicillin alone.

Patients treated with a combination of oleandomycin and penicillin had significantly fewer days of lower respiratory illness than patients treated with placebo and also fewer days of illness with fever than patients receiving penicillin alone.

Therapy with penicillin alone was no more effective than placebo therapy.

There was no significant reduction in sputum volume or purulence and no significant gain in weight or improvement in pulmonary function in patients on antibiotic therapy.

Tetracycline significantly reduced the frequency of isolation of Diplococcus pneumoniae (pneumococci) and coagulase-positive staphylococci from these patients. It reduced the frequency of isolation of Hemophilus influenzae but not significantly. Oleandomycin and penicillin, in combination, reduced the frequency at which coagulase-positive staphylococci were isolated.

Patients from whom H. influenzae was isolated had more days of lower respiratory infection than those patients from whom this micro-organism had never been isolated.

C-reactive protein decreased insignificantly in all groups.

Pulmonary function was not appreciably altered during the first year of therapy.

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The Use of Adrenal Steroids in Subacute and Chronic Cholangiolitic Hepatitis

A Clinicopathologic Correlation

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Introduction

Cholangiolitic hepatitis is a syndrome of varied etiology characterized by jaundice, pruritus, enlarged liver and spleen, and increased serum alkaline phosphatase and cholesterol. In some cases the onset of this syndrome can be traced to a viral type of hepatitis,[1-3] to drugs,[4] or to poisonous substances.[5] In other cases the etiology remains unknown. The parenchymal cells of the liver may be little affected, and important changes occur in the portal triads. The intralobular and perilobular bile canaliculi and ductules contain bile thrombi, and pericholangiolitis further complicates the histological picture. In protracted cases the differential diagnosis from extrahepatic biliary obstruction may be very difficult. Knowledge of this syndrome has increased, and liver biopsy has been helpful in avoiding unnecessary abdominal explorations. The management of chronic and recurrent cholangiolitic hepatitis has been a major problem. In some cases corticotropin (ACTH) and adrenocorticosteroids seemed of value. This paper describes four cases of subacute and chronic cholangiolitic hepatitis treated with steroids.

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Report of Cases

CASE 1.—A 50-year-old Negro man, when first seen, in September, 1956, had imbided ½ to 1 pt. of whisky daily for several years. He suffered from a bilateral chorioretinitis and was treated with bishydroxycoumarin (Dicumarol). Two months later he experienced bleeding from the gingiva and the urinary and gastrointestinal tracts and received two blood transfusions elsewhere.

TABLE 1.—*Liver-Function Tests in Case 1*

	1956								1957					1958
	9/4	9/10	10/24	10/31	11/16	11/26	12/5	12/14	1/7	3/22	6/10	9/14	11/29	2/1
Total protein	6.3				6.2	6.4	7.1	6.2						
Albumin	4.4				3.7	3.9	4.2	3.9						
Globulin	1.9				2.5	3.0	2.9	3.9						
Total bilirubin	3.1	3.4	2.8	2.8	5.1	2.3	1.5	0.9				0.4	0.4	0.5
Direct bilirubin	2.6	2.9	1.9	2.1	3.8	1.7	1.2	0.6				0.3	0.3	0.5
Alkaline phosphatase	8.6				6.1	6.6	5.9	4.6						1.3
Sulfobromophthalein, % retention	40								34.6	26	10			14
Cephalin-flocculation	3+		3+		4+	4+	3+	3+				2+	2+	3+
Thymol flocculation	Neg.											1+	2+	2+
Thymol turbidity	Neg.				5.6	5.6	5.6	3.1				6.2	10.8	13.5
Total cholesterol	205		175	185		290	300							325
Cholesterol esters	90													
Prothrombin time, %	90						100	100						
Urinary urobilinogen, mg/24 hr.					0.8			2.3						

Two months later he noticed general fatigue, anorexia, postprandial epigastric fullness, vague abdominal pains, and pruritus over the lower extremities. At physical examination the patient was rather obese; the sclerae appeared clear; the liver was palpable 5 cm. below the right costal margin and was smooth and somewhat tender. The liver-function studies revealed a total serum bilirubin of 3.1 mg. %, of which 2.6 mg. % was of the prompt-reacting variety; alkaline phosphatase was 8.6 units (Bodansky); sulfobromophthalein (Bromosulphalein) retention at 45 minutes was 40%. Other pertinent data are listed in Table 1. A liver biopsy revealed a mild fatty infiltration and enlarged portal areas, with a diffuse infiltration of lymphocytes and mononuclear cells. There were increased numbers of cholangioles at the limit between the periphery of the lobules and the adjacent portal areas (Fig. 1). The patient was treated with a high-protein, high-carbohydrate diet, vitamins, and bed rest. He did poorly at home. His appetite and strength decreased; the stools became lighter and the urine darker, and the pruritus recurred. On readmission, two months later, he had severe jaundice and scratch marks on the skin denoted the presence of pruritus. The liver was palpable 3 cm. below the right costal margin, and the spleen was palpable to the same extent. One smear of the peripheral blood was found positive for L. E. cells, but two subsequent smears were negative. The serum bilirubin was 5 mg. % total, with 3.8 mg. % prompt-reacting; the alkaline phosphatase was 6.1 units (Bodansky). A second liver biopsy revealed the same amount of cellular infiltration, cholangiolar proliferation, and minimal cellular damage (Fig. 2). Because of the protracted course of the disease and a predominance of mesenchymal

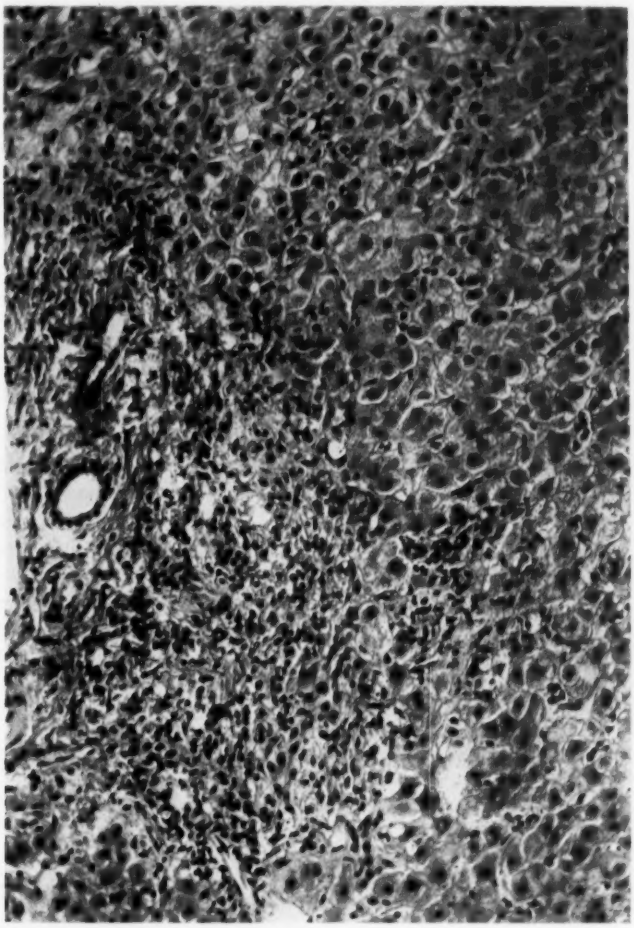

Fig. 1 (Case 1).—First biopsy. Large periportal area infiltrated with small round cells. Note proliferation of cholangioles and mild fatty infiltration. Reduced 10% from mag. × 280.

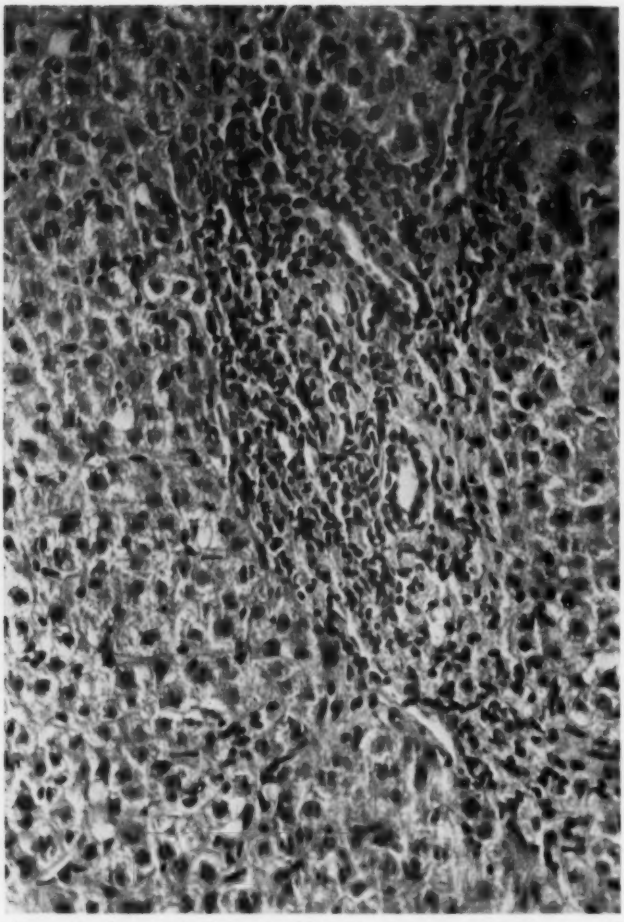

Fig. 2 (Case 1).—Second biopsy. Enlarged periportal area infiltrated with round cells. Note proliferation of cholangioles. There is some hydropic vacuolation and some fatty infiltration. Reduced 10% from mag. × 330.

changes in the portal triads, steroid treatment was started with 40 mg. of prednisone per day. There was a prompt and remarkable increase in appetite, with a feeling of well-being. The serum bilirubin and the serum alkaline phosphatase decreased to normal levels. At the same time the serum cholesterol increased to 390 mg. %. A third liver biopsy after three weeks of steroid therapy did not reveal significant changes (Fig. 3). The patient gained 17 lb. in a two-month period, felt fine, and had no pruritus. The amount of prednisone was gradually reduced. The patient currently is well and active. The sulfobromophthalein retention and serum cholesterol, now one and one-half years after the second admission, remain elevated, although less abnormal; the thymol turbidity is more abnormal than previously (Table 1).

Comment.—This 50-year-old man has a chronic cholangiolitic hepatitis. The alkaline phosphatase, significantly elevated initially, decreased later to normal, while the serum cholesterol, normal initially, continued to rise despite the steroid treatment. The flocculation tests remain positive, denoting perhaps the cellular damage possibly related to the use of alcohol. Steroids have increased the appetite and the sense of well-being. The decreased serum bilirubin and alkaline phosphatase may or may not be related to the adrenal steroids. Despite the clinical response there has been no demonstrable histologic evidence of improvement after three weeks of treatment with 740 mg. of prednisone.

Case 2.—A 63-year-old white woman was first admitted in April, 1957, with a history of recur-

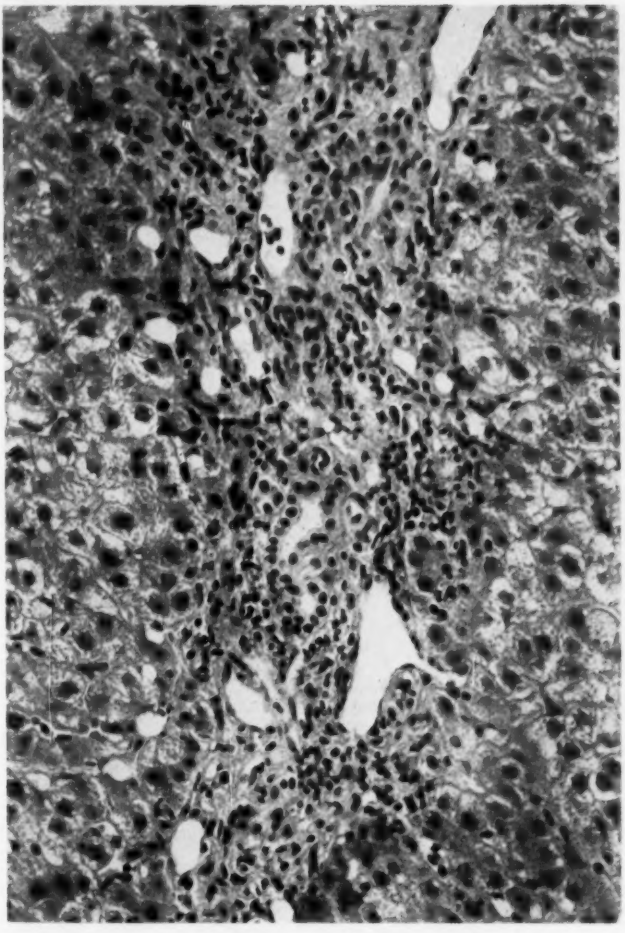

Fig. 3 (Case 1).—Third biopsy. The same amount of cellularity in the periportal area, more fatty infiltration, the same proliferation of cholangioles. Reduced 10% from mag. × 330.

rent episodes of diarrhea associated with lower abdominal pain of several years' duration. She also complained of midthoracic pain, low back pain, and frequent bouts of chills and fever. After many years of recurrent attacks of pain in the right hypochondrium, her gallbladder had been removed in 1946; chronic inflammation with stones was found. She was hospitalized at Cook County Hospital in June, 1953, with similar complaints. Parasites, "similar to amoebae," were found in one stool, and the patient was given diiodohydroxyquin (Diodoquin) and placebos. The discharge diagnosis was chronic colitis. During an extensive study elsewhere, in February, 1955, the only abnormal findings were a thymol turbidity of 13.8 units and cholesterol of 373 mg. %, but the final diagnosis was "psychophysiologic gastrointestinal reaction."

Physical examination at The University of Chicago, in April, 1957, revealed an obese woman with a blood pressure of 150/90. The liver was palpable three fingerbreadths below the right costal margin, with a round, firm, and somewhat tender margin. The laboratory tests revealed a normal blood cell count and normal blood chemistry. The blood carotene was 53μg. %, but rose to 120μg. % after three days of carotene orally. The Coombs test was negative. The glucose-tolerance curve was normal. The liver-function tests are recorded in Table 2. An intravenous cholangiogram demonstrated faint visualization of the common bile duct without evidence of stones. Duodenal drainage elicited normal values of enzymes and CO_2, but a culture of the drainage revealed the presence of coliform organisms and Pseudomonas aeruginosa. A liver biopsy dem-

TABLE 2.—*Liver-Function Tests in Case 2*

	1957							1958
	4/11	4/25	5/3	5/21	7/12	8/9	9/30	1/6
Total protein	8.8	7.4	7.5	7.4				6.5
Albumin	3.5	3.1	3.0	3.0				3.2
Globulin	5.3	4.3	4.5	4.4				3.3
Alkaline phosphatase	9.1	18.8	26.4	26.4	12.5		8.2	6.4
Sulfobromophthalein retention, %	34					31		
Total bilirubin	1.7	1.0	1.0	0.8	0.6			0.8
Direct bilirubin	1.1	0.8	0.7	0.16	0.4			0.5
Carotene, μg. %	53.7		120 After carotene orally					
Total cholesterol	310		255	290				360
Cephalin flocculation	4+		4+	4+				3+
Thymol turbidity	15.2		16.6	14.8				8.4
Thymol flocculation	3+		4+	4+				2+
Urinary urobilinogen, mg/24 hr.	1.2							1.85
Prothrombin time, %	92		97				82	80

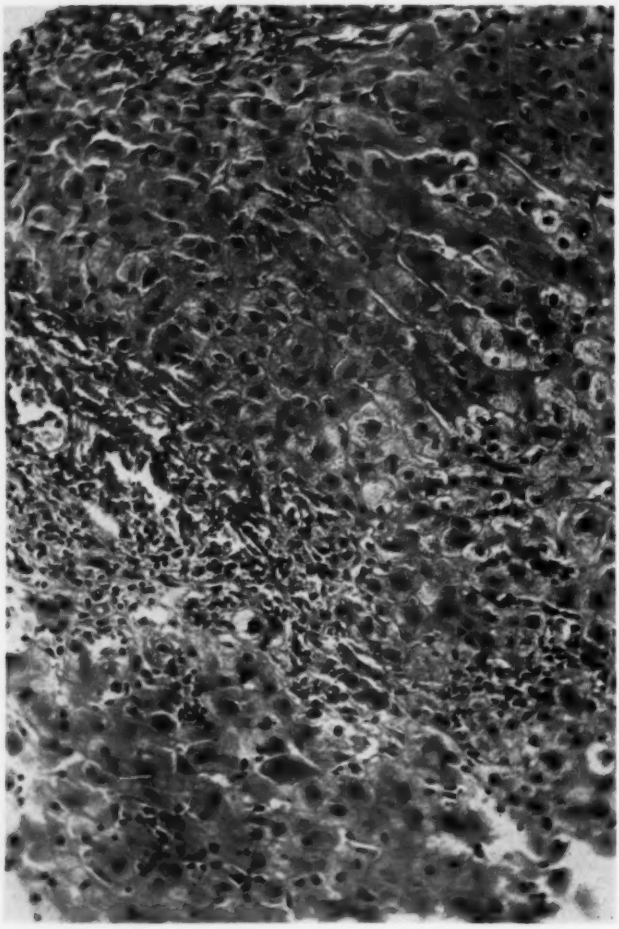

Fig. 4 (Case 2).—First biopsy. Enlarged periportal area with cellular infiltration and cholangiolar proliferation. Localized foci of necrosis in middle of parenchyma. Reduced 10% from mag. × 260.

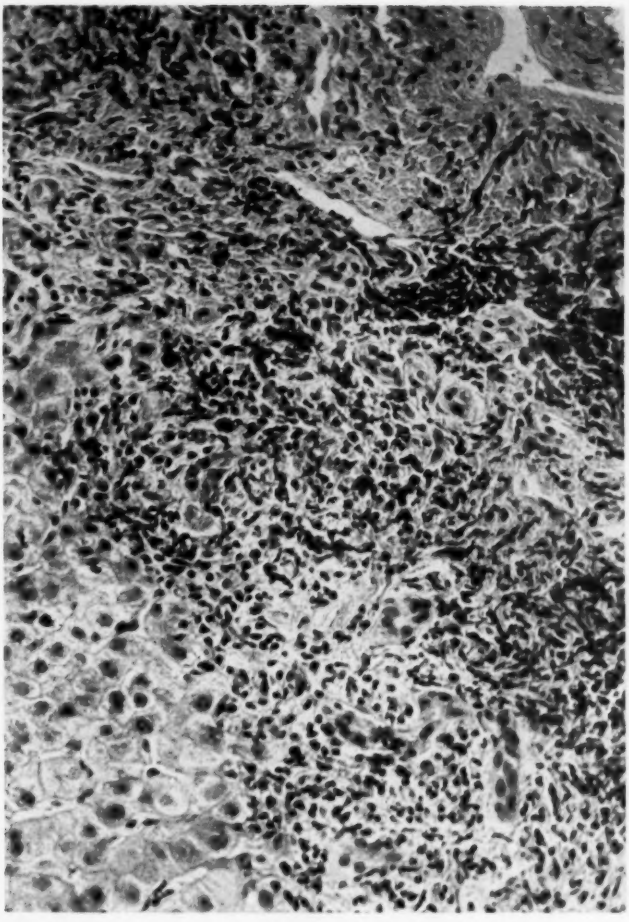

Fig. 5 (Case 2).—Second biopsy. Large area of fibrosis with lymphocytic infiltration; there are scattered polymorphonuclears, and there is a conspicuous proliferation of cholangioles. Reduced 10% from mag. × 330.

onstrated areas of cellular infiltration, with a limited number of proliferated cholangioles and polymorphonuclear cells (Fig. 4). The process was defined as pericholangiolitic hepatitis. The patient was given a high-protein and high-carbohydrate diet and treated also with rest, sulfadiazine, phenobarbital, and prednisone, 30 mg. a day. During the subsequent seven months her complaints did not change significantly. She described frequent spells of fever without chills, occurring once every two or three weeks. The temperature would rise to 102 F orally. There was obvious hypercortisonism, as evidenced by puffiness of the face and rise of the blood pressure to 190/110. The temperature rose to 102 F orally once in five days. The prednisone was reduced gradually to 10 mg. a day. She was readmitted for reevaluation in January, 1958.

The liver again was palpated 3 fingerbreadths below the costal margin, with a rounded firm margin. The liver-function tests indicated (last column of Table 2) a significant decrease in the globulins, thymol turbidity, and thymol flocculation tests. There was no change in sulfobromophthalein retention or total cholesterol. A second liver biopsy indicated still wider areas of cellular infiltration and proliferation of cholangioles (Fig. 5). Duodenal drainage again yielded coliforms and P. aeruginosa. The patient had no fever or diarrhea while in the hospital.

Comment.—This 63-year-old woman has a chronic cholangiolitic hepatitis of unknown etiology and unknown duration, possibly related to the previous gallbladder disease. She received a total of 5.5 gm. of prednisone orally for eight months. There has been obvious retention of water and elevation of the blood pressure. There has been no

change in the blood cholesterol or in sulfobromophthalein retention. While the flocculation tests, alkaline phosphatase, and serum plasma globulins decreased, histologically, the process remains as active as previously.

CASE 3.—A 63-year-old white man, first examined in January, 1957, apparently was in good health until September, 1956, when he developed pneumonia with pleural effusion. He subsequently complained of constipation and pain in the right upper abdomen, worse after eating and on motion. There had been no recent change in the color of the stools, but the urine had been darker; the appetite remained good, with no weight loss. His alcoholic intake had been negligible. Physical examination demonstrated an enlarged, tender liver. Laboratory examinations revealed an alkaline phosphatase of 9.6 units (Bodansky); serum cholesterol, 325 mg. %; albumin, 3.8 mg. %; globulin, 3.9 mg. %, sulfobromophthalein, 48% retention in 45 minutes; thymol turbidity, 6.8 units; cephalin-cholesterol flocculation, 4+ in 48 hours. Other pertinent examinations included x-rays of the esophagus, stomach, duodenum, colon, and terminal ileum, which were normal. In the course of four months of observation he gained weight and grew pale; the abdomen became distended, and he was admitted for further evaluation in May, 1957. The liver was 5 cm. below the right costal margin and not tender; the spleen was not palpated. There was suggestive evidence of ascites. The laboratory data after admission to the hospital are given in Table 3 (under May 24); L. E. cells were observed in a smear of the peripheral blood. X-ray examination of the chest revealed only fibrotic changes in both lower lungs and minimal blunting of the right costophrenic angle. A liver biopsy revealed severe infiltration of the periportal tracts, with pronounced proliferation of bile ductules, degeneration of hepatic cells, and bile retention. Large areas of liver were replaced by connective tissue, heavily infiltrated with small round cells, as in submassive necrosis (Fig. 6). The patient's condition deteriorated, with fever, increasing abdominal distention, and pleuritic pain necessitating analgesics. He received oxygen, antibiotics, and intravenous infusions of dextrose and pooled plasma. The abdomen became more distended, and the temperature rose to 40 C (104 F); he developed tachycardia and tachypnea. The patient received at this time chloramphenicol (Chloromycetin), erythromycin, and intravenous infusions of hydrocortisone, 100 mg. every 12 hours. On this program there was marked improvement, with return of the pulse and temperature to normal. Mental confusion and flapping tremor of hands were observed on one occasion. The patient remained improved for about two weeks; then, ascites and peripheral edema increased, and the hemoglobin fell to 9.4 gm. %. Blood transfusions were administered, and the hemoglobin rose to 11.2 gm. %. At this time laboratory examinations revealed lowered values of alkaline phosphatase, blood cholesterol, and bilirubin. The serum albumin was 2.2 gm. %. One month after admission hematemesis of approximately 50 cc. of blood supervened, and the patient lapsed into coma. His blood pressure fell to shock levels and responded temporarily to intravenous administration of levarterenol ([*l*-norepinephrine] Levophed). Drainage of gastric contents revealed a large amount of bright red blood. The patient died despite all therapeutic efforts. At autopsy there was an ascites of about 3 liters of fluid. Enlarged veins and evidence of bleeding points covered with clotted blood were found in the lower part of the esophagus. The liver was flabby and had a finely nodular surface, with nodules of 1-3

TABLE 3.—*Liver-Function Tests in Case 3*

	1957										
	1/16	2/25	3/25	5/3	5/24	6/3	6/6	6/10	6/14	6/17	6/24
Total protein	7.7			7.7	6.8	7.0	6.9	6.1		5.0	6.2
Albumin	3.8			2.7	2.8	2.6	2.7	2.7		2.2	3.7
Globulin	3.9			5.0	4.4	4.4	4.2	3.4		2.8	2.5
Total bilirubin	0.7				2.1	1.4	0.8	1.0	1.0	0.7	
Direct bilirubin	0.4				1.4	0.8	0.8	0.7	0.8	0.5	
Alkaline phosphatase	9.6	12.6	10.8	15.7	12.9	10.9	4.9	5.3	4.7		
Sulfobromophthalein retention, %	48				39						
Cephalin flocculation	3+			4+	4+	4+	4+	4+	4+	4+	
Thymol turbidity	6.8				12.7	13.1	13.5	11.1	8.1	7.4	
Thymol flocculation	Neg.			4+	4+	4+	4+	4+	4+	4+	
Total cholesterol	325				345	205		175	155	115	
Cholesterol esters											
Prothrombin time, %					80						
Urinary urobilinogen											

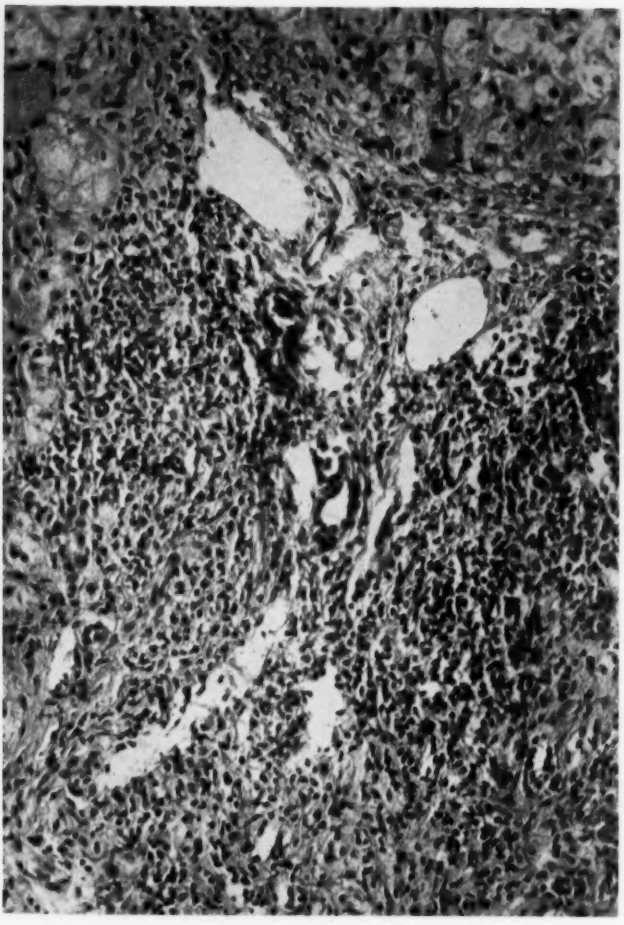

Fig. 6 (Case 3).—Large area of necrosis with replacement of connective tissue infiltrated with lymphocytes. Note cholangiolar proliferation and enlarged lymphatics. Reduced 10% from mag. ×265.

mm. in diameter. The lower portions of the lungs were firm, and there was frothy bloody fluid on the cut surface. Microscopic examination revealed submassive necrosis of the liver, with replacement of parenchyma with connective tissue heavily infiltrated by round cells. Bile duct proliferation (Fig. 7) was conspicuous in such areas, and lymphatics appeared dilated (Fig. 8). There were large bands of connective tissue originating in periportal areas and intersecting the parenchyma; there was a fatty degeneration at the periphery of liver lobules, bile retention in the liver cells, and bile plugs in intralobular bile ductules. The lungs contained areas of alveoli filled with edema fluid and erythrocytes. Other areas had emphysema.

Comment.—This is a case of a subacute fatal cholangiolitis in a 63-year-old man. The role of the past pneumonia in the onset of this disease can only be assumed. Moderately elevated values of alkaline phosphatase and cholesterol were repeatedly observed and later declined to normal and subnormal values. Excessive proliferation of cholangioles, with intense inflammation of periportal areas, was the main histologic feature. There also was hepatic-cell degeneration, bile stasis, and fibrosis. No nodular regeneration was present in the autopsy specimens, although portal hypertension with esophageal bleeding contributed significantly to death in hepatic insufficiency. The patient received 2,005 mg. of hydrocortisone in several weeks without beneficial effect upon the hepatic disease.

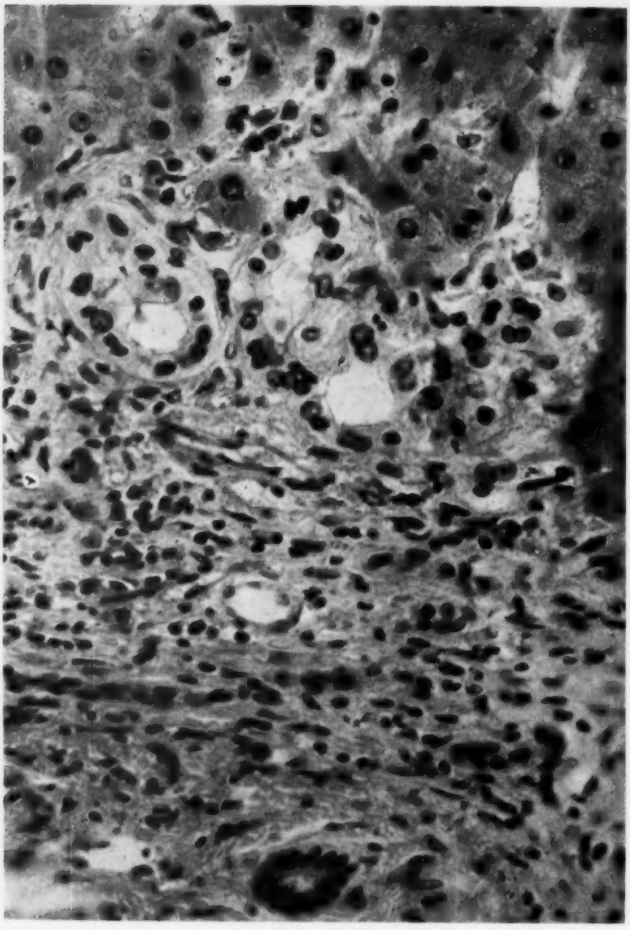

Fig. 7 (Case 3).—Periportal space; the fibrillar connective tissue is infiltrated with lymphocytes. Note ductular budding above center of the figure. The darkly stained polygonal hepatic cells show signs of biliary retention. Reduced 10% from mag. × 475.

Case 4.—A 40-year-old housewife was first seen in October, 1955. She had been in good health until July, 1955, when she passed several stools mixed with blood. She was hospitalized elsewhere and received several transfusions of blood, as well as liver and iron preparations, for an anemia. Proctoscopy and a gastrointestinal series revealed no abnormality. The icterus index was 25 units, and the patient was referred for further evaluation.

Physical examination demonstrated slight scleral icterus. The liver was barely palpable at the right costal margin, but at the midline it almost reached the umbilicus, where it was palpated as a firm and somewhat tender structure. The bilirubin was 2.2 mg. % total and 1.6 mg. % direct. The flocculation tests were positive. Jaundice of hepatocellular origin was suspected, and the patient, therefore, was admitted to the hospital. The liver was palpated 3 fingerbreadths below the costal margin. Liver-function studies revealed increasing jaundice and high values for plasma globulins, alkaline phosphatase, and total cholesterol (second column, Table 4). X-ray studies of the gastrointestinal tract, including an intravenous cholangiogram, demonstrated no abnormality. At proctoscopy, large internal and external hemorrhoids were noticed and thought to have been the source of the past bleeding. A liver biopsy revealed large areas of connective tissue, with marked cellular infiltration of lymphocytes and mononuclear cells. The hepatic cells were well preserved (Fig. 9). The pathological diagnosis was early cirrhosis resulting from a previous hepatitis or a primary cholangiolitic process. The patient was given a high-protein, high-carbohydrate diet, rest, and vitamins. During the three and one-half months following discharge the liver increased in size to 10 cm. below the right costal margin and became irregular. The plasma globulins increased

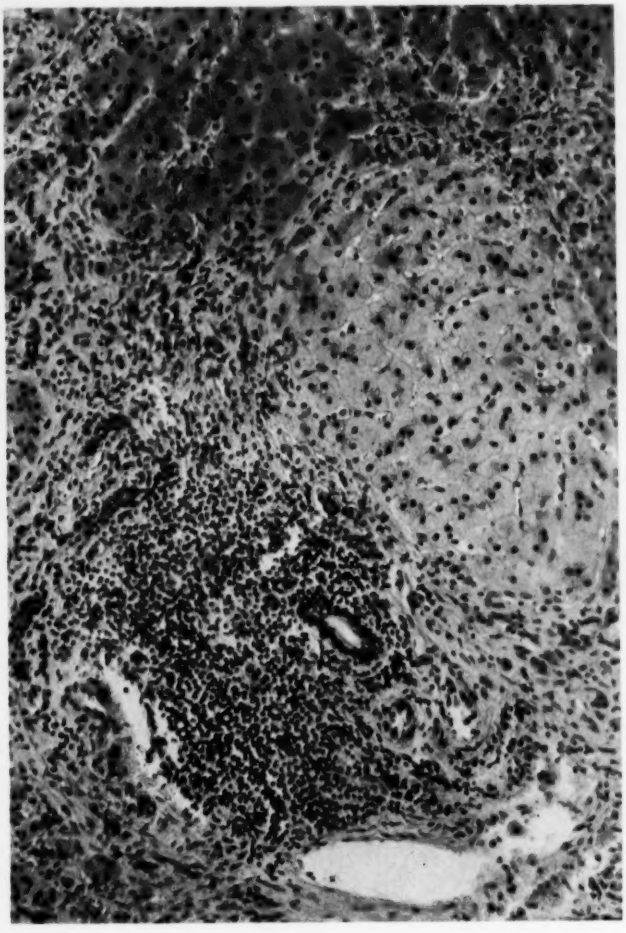

Fig. 8 (Case 3).—Note heavy lymphocytic infiltration, cholangiolar proliferation, liver-cell necrosis, and dilatation of lymphatics. Reduced 10% from mag. × 180.

TABLE 4.—*Liver-Function Tests in Case 4*

	1955				1956						1957			1958
	10/15	11/22	12/7	2/25	5/5	7/28	9/1	11/24	2/23	4/5	7/28	11/30	10/12	12/21	2/22
Total protein		8.4	8.5	8.9				8.4	8.1						8.1
Albumin		3.5	3.5	3.1				3.8	4.0						4.0
Globulin		4.9	5.0	5.8				4.6	4.1						4.1
Total bilirubin	2.2	2.8	2.2		1.3	3.4	2.4	2.6				3.2	6.5	2.4	3.0
Direct bilirubin	1.6	2.2	1.7		1.2	2.4	1.9	2.0				2.3	5.0	1.8	2.7
Alkaline phosphatase		33.7	45.7	51.1		45.4	15.8	27.3	28.2			28.2		18.3	20.3
Sulfobromophthalein retention, %		9								19					
Cephalin flocculation	3+	4+		2+				4+	4+	2+					Neg.
Thymol turbidity	6.7	10.2		17.8				7.7	3.4	13.7					5.6
Thymol flocculation	4+	4+		4+				3+	3+	3+					Neg.
Cholesterol, total		640			880	590			450			1,060	1,200		470
Cholesterol esters		385			590	280									270
Prothrombin time, %	88	99													
Urinary urobilinogen, mg/24 hr.		3.75													

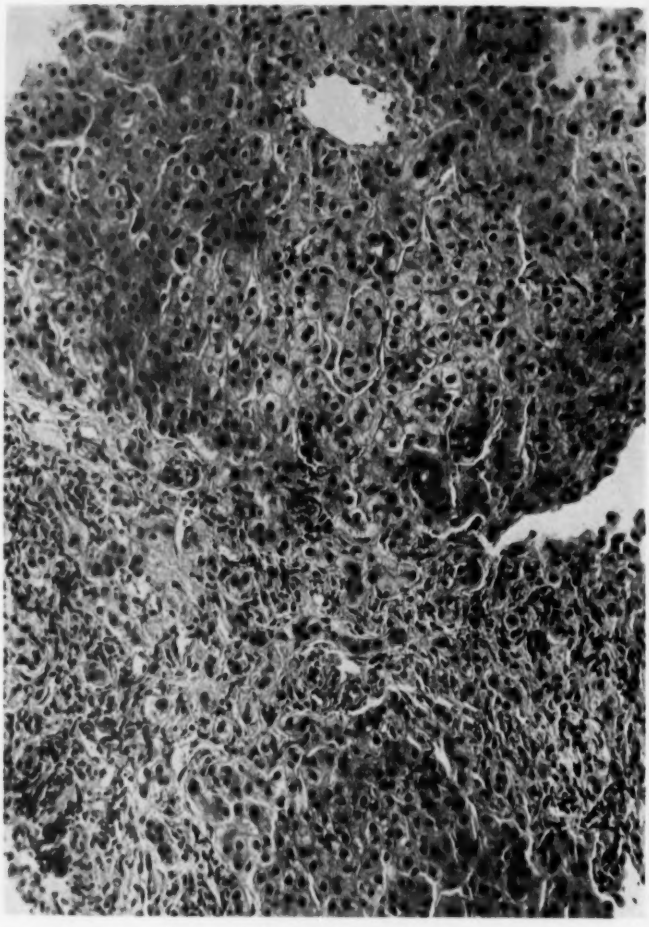

Fig. 9 (Case 4).—Large area of postnecrotic scarring. Isolated cells and groups of cells included in fibrous tissue. Liver lobules well preserved, one with its central vein. Reduced 10% from mag. × 225.

to 5.8 gm. % and alkaline phosphatase to 51 (Bodansky) units. Jaundice and anemia persisted (hemoglobin, 10.4 gm. %; erythrocyte, 3,370,000). At this point prednisone was prescribed, 30 mg. daily. The patient felt subjectively better, had a good appetite, and seemed stronger; at this time the cholesterol was 880 mg. %. She presented cholesterol deposits on the creases of the palms and in the eyelids. Her complexion grew tan, and she became puffy. The prednisone was gradually decreased to 5 mg. daily. At this level she noted generalized itching (which was present before the institution of prednisone [Meticorten] therapy), and the daily dose of 10 mg. was resumed.

The patient seemed to improve steadily during the winter of 1956-1957. The sclerae cleared, and the palmar deposits of cholesterol decreased. The total cholesterol at that time was 450 mg. %. At this point prednisone was discontinued (February, 1956). In June, 1956, she seemed to be in fairly good health. She arbitrarily then increased her activity. The patient returned on Oct. 12, 1957. She had no complaints, but the liver was much larger, and she was obviously icteric. The serum bilirubin was 6.5 mg. %; alkaline phosphatase, 35 (Bodansky) units, and the total cholesterol, 1,200 mg. %. She declined rehospitalization for economic reasons and again was placed on prednisone, 30 mg. a day, together with bed rest and ordinary dietary measures. She is improving slowly. The patient has refused a repeat liver biopsy.

Comment.—This patient is suffering from a cholangiolitic type of biliary cirrhosis, which probably developed following a cholangiolitic type of homologous serum jaundice. Steroids induced an increase in appetite and sense of well-being and probably de-

creased the itching. The side-effects were water retention and some tanning of the skin. The steroid treatment did not prevent the rise in serum cholesterol level and the skin deposits of cholesterol, evidence that the underlying disease process was unaffected.

Comment

The physiologic effects of adrenal steroids on the liver are complex and vary, probably, from animal to animal.[6] Protein anabolism is inhibited in the carcass,[7] and seemingly there is a transfer of amino acids from the carcass to the viscera. The livers of treated animals were larger and contained more protein nitrogen than controls.[8] Administration of cortisone to animals treated with carbon tetrachloride prevented fibrosis of the liver.[9] Cortisone similarly delayed the mesenchymal response to foreign bodies implanted into the liver of rats.[10] Degeneration of the liver due to yeast feeding was delayed in the experimental animal,[11] probably because of intensified neoglucogenesis [12] caused by cortisone.

Clinically corticotropin and steroids have been prescribed in various hepatic diseases without uniform results. In hepatic coma no influence was observed [13] on the disease course or only temporary improvement in a few patients.[14] In our experience, steroids were helpful in bringing patients out of coma due to liver cirrhosis on two occasions and failed to do so in a case of coma terminating a severe acute hepatitis.[15] Ducci [16] observed good results in a group of five patients. Beneficial effects have been noted in severe cases of acute hepatitis.[17,18] In chronic liver disease corticotropin and steroids produced various effects. Hanger and Collins [19] observed in liver cirrhosis a decrease in the size of the liver and spleen, a reduction in the serum bilirubin and globulin, and an increase in the serum albumin; there was no change in serum alkaline phosphatase or sulfobromophthalein retention. Histologically, there was decrease in cellular infiltration. Havens et al.[20] noticed an increase in the sense of well-being and in appetite and a gain in weight; however, liver-function tests did not improve correspondingly. Suzman [21] observed a temporary decrease in the degree of jaundice but no change in liver tests. There again was no alteration in the histological appearance of liver tissue obtained while patients were under treatment. Sborov et al.[22] observed lack of improvement or relapses after discontinuance of steroid therapy; the course of hepatic cirrhosis was unchanged. Caroli and Delattre [23] treated 35 patients with acute and prolonged hepatitis with prednisone and found it useful in most instances; they advocate the use of the drug in all cases. Wildhirt [24] observed improvement in portal cirrhosis in two-thirds of 28 cases; there was an increase in serum albumin and a decrease in the inflammatory activity, as evidenced by liver biopsies.

Johnson and Doenges [25] reported dramatic improvement with corticotropin and steroids in cholangiolitic hepatitis of viral origin. Lipschutz and Capson [26] also advocate these drugs in intrahepatic cholestasis. Albot [27] found the corticoids valuable in chronic cholangiolitis, promoting a general sense of well-being and a delay in the progression of the disease. No change was noted in most liver tests, and the cirrhosis was not altered significantly.

In the present group of four patients, there was an increase in appetite and in the sense of well-being shortly after the onset of steroid therapy in Cases 1, 2, and 4. In Case 3 the temperature and pulse decreased to normal levels without delaying the fatal course of the disease. Itching disappeared in Cases 1 and 4. Definite signs of water retention were noted in Cases 1, 2, and 4; there was no significant change in liver size.

There was a remarkable decrease in bilirubin in Case 1 and a very questionable change in Case 4. In Cases 2 and 3 bilirubin values were very low, and no definite conclusions can be drawn. Decreases in serum bilirubin during steroid therapy have been observed repeatedly and variously explained. Patterson et al.[28] suggested a choleretic action with promotion of bile synthesis.

Shay and Sun[29] could not confirm this theory when the bile was collected through a T-tube in postcholecystectomy patients. Mainguet and Caroli[30] studied the effect of prednisolone on the blood bilirubin and fecal urobilinogen and suggested as a mechanism for the rapid-emptying steroid effect of the ampullary portion of the bile ductules, which fill later with bile slowly enough to cause a secondary drop in the fecal urobilinogen curve. The anti-inflammatory action of steroid certainly explains best the rapid liberation of bile from the tiny compressed bile ductules. The present observations cannot be interpreted in support of any of the theories.

The serum albumin remained unchanged in Cases 1 and 2; decreased in Case 3, probably because of the rapidly failing liver, and slightly increased in Case 4. Albumin is produced mainly in the liver and may serve as an indication of the state of the liver parenchyma in chronic liver disease. There was no change in the serum globulin level in Case 1, but there were decreases in Cases 2, 3, and 4 under steroid treatment. In Case 2 the decrease was from 5.3 gm. % to 3.3 gm. %. In Cases 3 and 4 the globulins reached an elevation of 5 gm. %. No separation was made of the various components of the globulin fraction.

The serum alkaline phosphatase is particularly increased in the cholangiolitic form, as compared with the hepatocellular type of liver disease. There was a decrease in Cases 1 and 4 and a significant elevation in Case 2 in spite of treatment and then a slow decline. In Case 3 the alkaline-phosphatase level persisted, increased for some time, and then declined, indicative of the final failure of the liver. It is thought that cholangiolar regeneration may account[31] for the raised levels of this enzyme in cholangiolitic types of liver disease.

The total cholesterol was elevated significantly in all four cases. In Cases 1, 2, and 4 there was a rise in cholesterol level despite steroid treatment. At the same time there was a decline of alkaline phosphatase. This dissociation of steroid action is most pronounced in Case 4. Alkaline phosphatase and total cholesterol, both elevated in cholangiolitic hepatitis, behave differently under steroid therapy. This point does not seem to have been sufficiently stressed in the literature, though the failure of cortisone to depress blood cholesterol in essential hyperlipemia has been observed.[32] This point deserves further study.

There was no change in cephalin-cholesterol flocculation under steroid treatment in Cases 1, 2, and 3 and possibly a decrease over a prolonged period of time in Case 4; the length of time for the change to take place makes it doubtful if it has anything to do with steroid treatment. Thymol-turbidity and thymol-flocculation tests were equally unaffected by the steroid treatment.

L. E. cells were found in two patients. Both cases do not resemble the series of so-called lupoid hepatitis described by Mackay.[33] Neither did we observe the beneficial effect of steroids in these cases, as reported for lupoid hepatitis. Nevertheless, we would be inclined to agree that the L. E. cells in such cases might be indicative of an immunological disturbance in this type of hepatitis.

There has been no change in the various features of the liver biopsy specimen in Case 1 and a worsening of the histological picture in Case 2 despite steroid therapy. In Case 3 death permitted a more thorough examination of the extension and severity of the disease; the liver biopsy specimen obtained in Case 3 one month prior to death had given a good indication of the gravity of the disease process. Repeated biopsy specimens could not be obtained in Case 4, but there is conclusive clinical and laboratory evidence of the persistence of the disease process. These results conform to previous observations[20] and suggest that the improvement observed by others[20,28] may be attributed to the variable degree of pathological changes present in chronic hepatitis.[20]

Summary

Four cases of chronic cholangiolitic hepatitis treated with adrenal steroids are de-

scribed. The clinical symptoms, the liver-function tests, and the histopathological findings during the steroid treatment are summarized and briefly discussed. There has been an increase in appetite and in the sense of well-being and a decrease of itching. Bilirubin and globulin values decreased in some cases. There has been an interesting dissociation of alkaline phosphatase and cholesterol levels under steroid treatment, with a decrease of the former and an increase of the latter. Other liver-function tests remained unaffected. There has been no change in the histopathology of the disease process.

Conclusion

Adrenal steroids do not seem to affect the basic disease process in chronic and subacute cholangiolitic hepatitis.

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The Use of Chlorothiazide in the Nephrotic Syndrome

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The new diuretic agent, chlorothiazide (6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide),* is useful in the treatment of many clinical disorders, including congestive heart failure, cirrhosis, nephrosis, essential hypertension, premenstrual edema, and toxemia of pregnancy.[1-9] Among its various clinical advantages are (1) remarkable effectiveness when administered orally; (2) prompt diuretic action, consisting of water diuresis, natruresis, and chloruresis but only minimal kaluresis; (3) persistent activity and lack of tolerance until edema subsides; (4) antihypertensive action, and (5) minimal side-effects or toxic reactions.

Basic pharmacologic studies have demonstrated that chlorothiazide inhibits carbonic anhydrase in vitro but not significantly in vivo,[2] and clinical trials in man indicate that its diuretic action is qualitatively similar to that of the mercurial diuretics. In short-term animal experiments,[1] maximal diuresis was observed at 40 minutes after intravenous administration, with a total duration of effect of about 4 hours. The peak response after oral administration occurred at 4 hours, with a total duration of about 12 hours. The diuretic response could not be attributed to a change in glomerular filtration rate but appeared to be due to decreased tubular reabsorption of water, sodium, and chloride.

Quantitative studies of electrolyte excretion revealed the excretion of sodium and chloride to increase five- to tenfold, whereas that of potassium was less than double the control value.[1] With large dosages (2 gm. daily), excretion of ammonia was depressed, that of phosphate was unaffected, and that of bicarbonate was increased, reflected by a rising pH of urine, which began to decline after four hours. Excretion of chloride always greatly exceeded that of bicarbonate.

In prolonged clinical studies, Laragh[2] found chlorothiazide to be effective in the treatment of congestive heart failure secondary to arteriosclerotic and rheumatic heart disease and cor pulmonale, as well as cirrhosis and nephrosis. In all patients, the level of potassium in the serum decreased after treatment,[2,7,8] with development of mild to moderate hypochloremic alkalosis.[2] The hypokalemia was frequently asymptomatic and relatively refractory to administration of supplemental potassium chloride.[8] Excretion of potassium appeared to be greater in the patients without significant excretion of sodium.[2] Chlorothiazide produces asymptomatic hyperuricemia, but the mechanism is unknown.[2]

Approximately 1 gm. of oral chlorothiazide has a diuretic action equivalent to that of 1 cc. of meralluride (Mercuhydrin) given intramuscularly, and 500 mg. has the diuretic effect of 40 mg. of oral chlormerodrin (Neohydrin). Chlorothiazide is twice as potent as acetazolamide (Diamox).[1]

The diuretic action continues, without evidence of clinical tolerance, until all edema is lost.[1] Maximal diuretic effect is achieved with a dosage of 2 gm. daily in four divided doses. Hemoglobin, erythrocytes, white blood cells, platelets, and liver function have not been altered by chlorothiazide, and gastrointestinal symptoms have been negligible.

Chlorothiazide alone, in a dosage of 0.5 gm. three times daily, has been reported to

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* Diuril, supplied by Merck Sharpe & Dohme, West Point, Pa.

be effective in the treatment of nonedematous patients with essential hypertension, and when it is given to patients with other agents (ganglionic blocking agents, reserpine, and hydralazine) the dose of these drugs can be reduced.[3,5] A minor initial loss of weight secondary to temporary diuresis at onset of therapy has been restored, even after prolonged, continuous therapy, although the level of sodium, chloride, and potassium in the serum has remained slightly depressed. Although retention of fluid was not clinically evident in the patients with essential hypertension whose blood pressure was reduced by chlorothiazide, the fact that the antihypertensive effect could be abolished by increasing the intake of salt would indicate that the mechanism of the antihypertensive effect may be concerned with natruresis.[3] Others have found that the antihypertensive effect obtained with combined therapy with ganglionic blocking agents may be due to decreased urinary excretion of these agents.[6]

Chlorothiazide, in doses of 0.5 gm. twice daily, was found by Finnerty and co-workers[4] to be extremely effective in the treatment of 144 patients with toxemia of pregnancy. In the mild cases, with edema as the sole manifestation, the diuretic response was good and the patients remained normotensive. In severe cases, chlorothiazide resulted in diuresis and reduction of hypertension and output of urinary albumin, with complete clearing of albuminuria in some instances. No untoward reactions were reported.

The present report is concerned with the study of the effect of chlorothiazide in the management of the nephrotic syndrome, with observations of the time-course of electrolyte and water excretion. The drug has proved to be extremely useful as a diuretic agent in the patient studied, even after other diuretic measures failed and plasma albumin concentration remained low.

Material and Methods

Ten patients from the Charity Hospital, in New Orleans, were selected for study on the basis of having nephrotic type of edema secondary to renal disease. The diet (2,200 Cal.) of all patients contained a constant known intake of electrolytes (1.5 gm. of sodium) and of protein (78 gm.). Twenty-four-hour specimens of urine were collected daily, with toulene as a preservative. Samples of blood were drawn every two or three days during the study. Whole venous blood was obtained with the use of heparin as an anticoagulant, and hematocrit tubes were filled at the bedside and centrifuged at 3,000 rpm for 30 minutes. A second sample of blood was collected under oil with the same needle from which the serum was obtained later.

The sodium and potassium levels of whole blood, serum, and urine were determined by means of a Beckman Du Flame Spectrophotometer. Chloride was measured by the method of Schales and Schales[10]; creatinine, by the method of Haugen and Blegen,[11] and osmolarity, by freezing-point depression method (Fiske Osmometer). Electrolyte and water clearances were calculated by conventional methods.[12,13]† Renal biopsies were done according to the method of Merrill,[14] Bouin's solution being used as a fixative.

Report of Cases

Case 1 (Acute exacerbation of chronic glomerulonephritis with the nephrotic phase).—A 16-year-old girl first noticed dark urine and generalized edema in August, 1957. Bed rest, low-sodium diet, administration of prednisone daily, and ammonium chloride resulted in little relief of edema.

On admission, on Nov. 7, 1957, she had generalized edema, ascites, and normal blood pressure. Results of laboratory studies were as follows: packed cell volume 35%; WBC and differential normal; urine was coffee-colored, with specific gravity 1.022, albumin 4+, sugar negative, innumerable red and white cells, many coarse granular casts; serum albumin 1.6 gm. per 100 ml.; serum cholesterol 218 mg. per 100 ml. Other laboratory data were not significant. Acute proliferative and membranous glomerulonephritis was the pathologist's interpretation of the renal biopsy.

After control studies, the patient was given 0.5 gm. of chlorothiazide twice daily. The diuretic response was remarkable in that she lost 24 lb. in nine days and appeared and felt considerably better (Fig. 1). She was discharged edema-free, on a mainetenance dose of 250 mg. of chlorothiazide daily. When seen three months later, she had no edema or evidence of electrolytic imbalance, al-

† Osmolar water clearance, $Cosm = \frac{Vosm\ V}{Posm}$. Total water clearance, V = volume of urine excreted per minute. Free water clearance is the difference between total water clearance and osmolar water clearance.

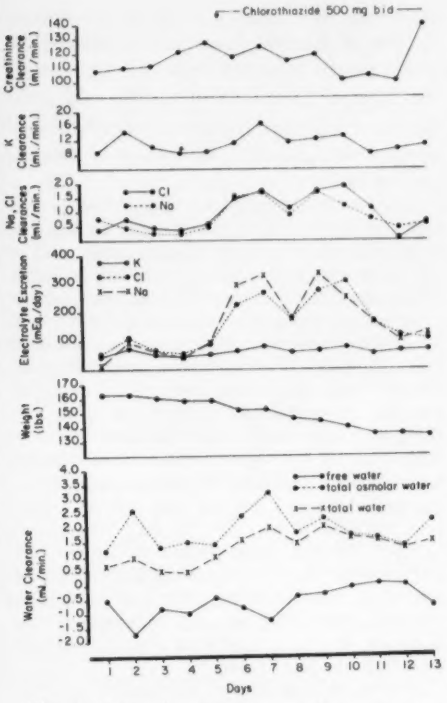

Fig. 1 (Case 1).—Excretory patterns of water and solute in a 16-year-old Negro girl with chronic nephritis with the nephrotic syndrome. Excretion of sodium, chloride, and osmolar water increased with administration of chlorothiazide, but excretion of potassium was unchanged.

though the urine and hypoproteinemia were unchanged.

Comment.—This patient with a clinical picture of chronic glomerular nephritis with the nephrotic syndrome and superimposed acute exacerbation was extremely edmatous and had failed to respond to conventional therapy. The response to chlorothiazide was dramtic. The urinary clearance of Na, Cl, and water increased promptly and essentially proportionately. Relatively little K was lost (Fig. 1). Water was lost by means of osmotic diuresis, i. e., excretion of concentrated urine.

The serum proteins and creatinine clearance remained unchanged throughout. The patient was considerably improved clinically, which may not have been related to any beneficial influence of the drug on the pathologic process in the kidney.

CASE 2 (Chronic glomerulonephritis of the nephrotic phase).—A 30-year-old woman noticed the appearance of ascites and periorbital and pedal edema in 1955, when she was found to have 4+ albuminuria, hypoalbuminuria, blood pressure 140/100 mm. Hg, and normal blood urea nitrogen, hematocrit, excretion of phenolsulfonphthalein, electrocardiogram, and roentgenogram of the chest. The edema and albuminuria failed to respond to conventional therapy for two years.

Massive edema, ascites, and blood pressure of 130/90 mm. Hg were the only significant signs on this admission. Pertinent laboratory data were as follows: WBC 12,500 (normal differential); urine showed specific gravity 1.021, albumin 3+, 10 to 15 WBC and numerous fine and coarse granular casts; serum cholesterol 1,145 mg. per 100 ml.; serum protein A/G ratio 0.72:2.61 gm. per 100 ml.; blood urea nitrogen 28 mg. per 100 ml. Other laboratory data, including serum electrolytes, were normal. The diagnosis of acute proliferative membranous glomerulonephritis was found on renal biopsy.

Treatment with bed rest, low-sodium diet, and prednisone, 40 mg. daily, had no effect, but administration of chlorothiazide, 0.5 gm. twice daily, produced dramatic diuresis (16 lb. lost in seven days), with little change in serum proteins, cholesterol, or urinalysis.

CASE 3 (Kimmelstiel-Wilson syndrome).—A 27-year-old man had diabetes for 14 years, which had been treated with 50 units of protamine zinc insulin daily. During the 18 months preceding admission, he had been troubled by impaired vision and mild edema. Three months before admission, weakness, ascites, and midabdominal pain developed.

Significant findings were as follows: blood pressure 190/110 mm. Hg; diabetic retinopathy; ascites; massive edema; mild neuropathy of the legs; WBC 12,500 (normal differential); urine was acid, with specific gravity 1.009, albumin 4+, sugar negative, acetone negative; serum protein A/G ratio 2.52:2.62 gm. per 100 ml.; maximal urinary concentration 1.011; blood urea nitrogen 31 mg. per 100 ml.; intravenous pyelogram normal except for delayed excretion; fasting blood sugar 104 to 495 mg. per 100 ml. and cholesterol 317 mg. per 100 ml. All other laboratory data were normal. The diagnosis of diabetic glomerulosclerosis was made on renal biopsy.

Intramuscular injection of 1 ml. of a mercurial diuretic resulted in only a mild diuretic response (loss of 7 lb. of weight in six days) (Fig. 2). Administration of chlorothiazide, 0.5 gm. twice daily, caused a loss of 13 lb. of weight in five days. The patient was discharged, edema-free, on a maintenance dose of 250 mg. of chlorothiazide daily and a low-sodium diet.

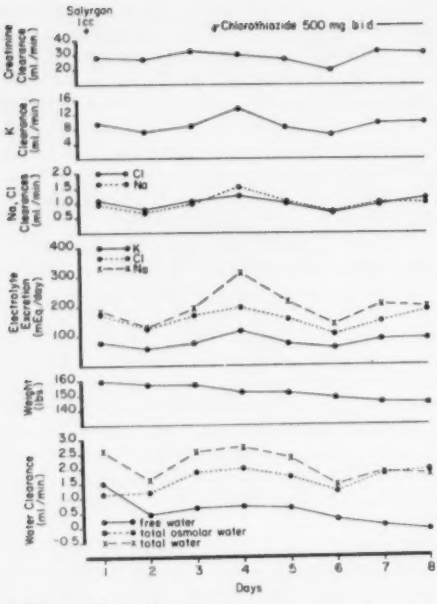

Fig. 2 (Case 3).—Excretory patterns of water and solute in a 27-year-old white man with Kimmelstiel-Wilson syndrome. Chlorothiazide produced a greater excretion of sodium, chloride, and osmolar water than did mersalyl sodium (Salyrgan), which produced greater free water diuresis.

Because of reaccumulation of edema as a result of insufficient sodium restriction, however, he required readmission six weeks later, at which time chlorothiazide was discontinued. A mercurial diuretic used on this admission was more effective than chlorothiazide when given again after one week. The concentrations of serum electrolytes were normal after eight weeks of treatment with chlorothiazide.

Comment.—In this patient with severe diabetic glomerulosclerosis, the diuretic reponse to the first course of chlorothiazide was superior to the single injection of a mercurial diuretic. The diuresis was accompained by a pronounced increase in urinary excretion of sodium and chloride but minimal increase in excretion of potassium (Fig. 2). Clearances of sodium, potassium, and chloride were increased at onset of administration of chlorothiazide. The entire diuresis, except in the terminal period of the study, consisted of excretion of "free water," the urine having a specific gravity less than 1.010. The "free water" diuresis was relatively greater in response to the mercurial diuretic than to chlorothiazide, which produced a relatively greater loss of electrolytes. On the second admission, some degree of tolerance had apparently developed to chlorothiazide but the mercurial diuretic was effective.

Case 4 (Chronic glomerulonephritis of the nephrotic phase).—A 16-year-old girl had transient episodes of edema at 8 and 13 years of age, each of two weeks' duration. One month before admission (November, 1957), persistent edema developed.

Generalized edema and ascites, pale oral mucosae, Grade III retinopathy, blood pressure of 210/130 mm. Hg, and mild cardiac enlargement were observed. Hematocrit was 18%; WBC and differential, normal; urine reaction was acid, with specific gravity 1.005, sugar negative, 20 to 30 RBC, clumps of white cells; urine culture, Staphylococcus pyogenes var. aureus on three occasions; cholesterol 504 mg. per 100 ml.; blood urea nitrogen 42 mg. per 100 ml.; creatinine 5 mg. per 100 ml.; serum protein A/G ratio 1.76: 2.85 gm. per 100 ml.; roentgenogram of the chest, generalized cardiac enlargement and left pleural effusion. Other laboratory data were normal. The diagnosis of chronic sclerosing glomerulonephritis was made on renal biopsy.

Diuresis did not follow low-sodium diet, bed rest, two blood transfusions, repeated injections of

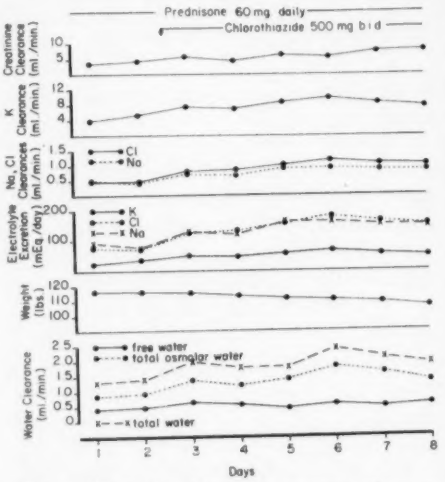

Fig. 3 (Case 4).—Excretory patterns of water and solute in a 16-year-old Negro girl with chronic glomerulonephritis with the nephrotic syndrome in whom diuresis could be produced only by chlorothiazide. Free water diuresis and increased excretion of sodium and chloride, with minimal increase in excretion of potassium, occurred after administration of chlorothiazide.

mercurial diuretics, prednisone (60 mg. daily), infusions of serum albumen (350 cc.), or treatment of the urinary tract infection. Chlorothiazide, 0.5 gm. twice daily, produced satisfactory diuresis (13 lb. of weight lost in seven days) (Fig. 3). The facial edema (Cushingoid facies) was resistant to chlorothiazide and resolved only after the dosage of prednisone was slowly reduced to 5 mg. daily. The blood urea nitrogen remained unaltered during diuresis, but a minimal change in serum protein A/G ratio occurred (from 2.48:1.84 to 2.96:2.33 gm. per 100 ml.) after diuresis. The blood pressure dropped significantly from 210/130 to 180/80 mm. Hg while the patient was receiving reserpine and chlorothiazide. When she was discharged, she was edema-free and greatly improved symptomatically. One month later, she had still maintained her "dry" weight while receiving 0.25 gm. of chlorothiazide daily, but the urine and serum proteins were unaltered.

Comment.—Chlorothiazide produced diuresis in this patient with severe nephritis after all other measures failed. An increase in the clearance of sodium, chloride, water, and creatinine were sustained for five days, with little increase in excretion of potassium (Fig. 3). This case demonstrates the antihypertensive effects of chlorothiazide, as well as its ineffectiveness in reducing the facial edema produced by steroids. The extremely low creatinine clearance cannot be explained.

CASE 5 (Amyloid disease of the kidney).—A 63-year-old man, was seen in 1955, when he was observed to have the nephrotic syndrome. The diagnosis of renal amyloidosis secondary to chronic osteomyelitis was made by renal biopsy in 1957. The patient was troubled with edema of increasing severity, which gradually became refractory to low-salt diet, mercurial diuretics, acetazolamide, and prednisone, and he was admitted for chlorothiazide therapy.

He had massive edema of the legs and back, blood pressure of 98/48 mm. Hg, and mild generalized weakness. Hematocrit was 39%; WBC 14,250 (normal differential); urine was acid, with specific gravity 1.012, albumin 4, and numerous WBC and granular casts; phenolsulfonphthalein 30% in 120 minutes; maximal urine concentration 1.015; blood urea nitrogen 20 mg. %; cholesterol 1.110 mg. per 100 ml.; protein A/G ratio 0.88:3.20 gm. per 100 ml.; serum sodium 132 mEq. per liter; potassium 2.8 mEq. per liter; chloride 106 mEq. per liter. Other laboratory data were normal.

After injection of a mercurial diuretic, the patient's weight increased, but administration of chlorothiazide initiated slow but steady diuresis. The low level of serum potassium (believed to be due to repeated injections of mercurial diuretics before admission) increased during administration of chlorothiazide, but because of some increase in urinary excretion of potassium, supplemental potassium chloride was given. The serum proteins, blood urea nitrogen, cholesterol, and urinary excretion of protein were unchanged after the patient reached a state of normal hydration. The serum electrolytes have remained normal after eight weeks of treatment with chlorothiazide.

Comment.—This patient with proved renal amyloidosis had the classical picture of the nephrotic syndrome with edema refractory to conventional therapy. Potassium depletion had developed. Chlorothiazide produced increased excretion of Na and Cl but minimal increase in excretion of potassium (Fig. 4). Plasma clearances of sodium,

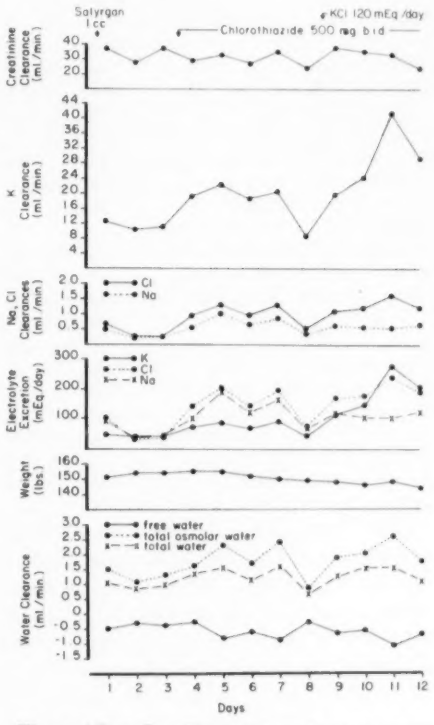

Fig. 4 (Case 5).—Excretory patterns of water and solute in a 63-year-old Negro man with renal amyloidosis in whom mercurial diuretics failed to control the edema and had caused potassium depletion. Chlorothiazide, however, did produce increased excretion of sodium, chloride, and osmolar water. Supplemental potassium was given even though the kaluresis was not excessive.

chloride, and potassium were increased coincident with administration of chlorothiazide. Throughout the entire diuretic period there was "osmolar water diuresis," with urinary specific gravity consistently above 1.015.

CASE 6 (Chronic glomerulonephritis of the nephrotic phase).—A 43-year-old longshoreman had edema, ascites, and orthopnea in May, 1957. He was normotensive and had a reversed A/G ratio, mild azotemia, and albuminuria. Treatment consisted of low-sodium diet, digitalis, weekly injections of mercurial diuretics, and intermittent administration of acetazolamide, all without effect on the edema. He finally required admission.

He was found to have generalized edema and ascites, blood pressure of 145/98 mm. Hg, mild cardiomegaly, and hepatomegaly, with hemorrhages and arteriolar constriction in the optic fundi. The hematocrit was 30%; WBC 12,000 (normal differential); urine was acid, with specific gravity 1.012, albumin 4+, numerous red and white cells and granular casts; urine culture showed Aerobacter; blood urea nitrogen 34 mg. per 100 ml.; creatinine 2.8 mg. per 100 ml.; serum protein A/G ratio 0.96:5.44 gm. per 100 ml.; fasting blood sugar 94 mg. per 100 ml.; cholesterol 244 mg. per 100 ml.; venous pressure 140 mm. H_2O. Other laboratory data were normal. The diagnosis of chronic glomerulonephritis was confirmed on renal biopsy.

After bed rest, low-sodium diet, and mercurial diuretics were without effect, the patient was given 0.5 gm. of chlorothiazide only twice daily for four days, during which time he lost 18 lb. Mercurial diuretics were tried again, with only negligible effect, but another course of chlorothiazide was effective, with loss of an additional 16 lb. in 10 days (Fig. 5). The blood urea nitrogen rose as dry weight was approached and declined to its previous value after administration of chlorothiazide was discontinued and fluid reaccumulated. During the period of increased blood urea nitrogen, the creatinine clearance was essentially unchanged.

Comment.—Chlorothiazide produced a greater water diuresis than the mercurial diuretic but did not produce as great an elevation of sodium and chloride clearance (Fig. 5) The increase in clearances of Na, Cl, and free water coincident with administration of KCl may have been related to the replenishment of cellular potassium and correction of a potassium deficiency. When administration of chlorothiazide was started and that of potassium was discontinued, the high clearance levels persisted but the water

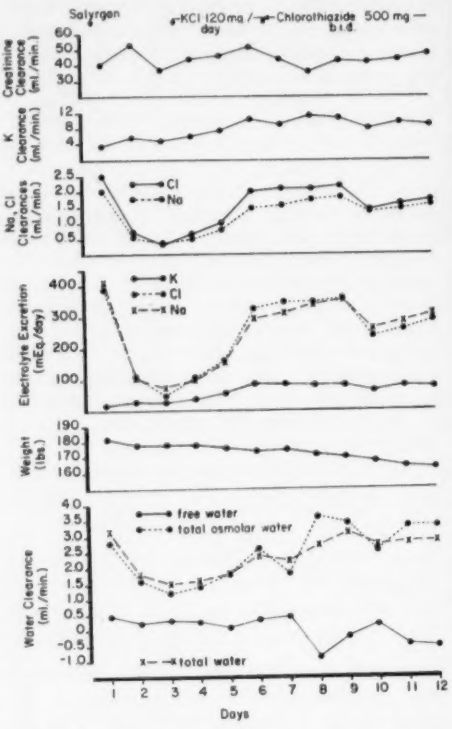

Fig. 5 (Case 6).—Excretory patterns of water and solute in a 43-year-old Negro man with chronic nephritis in whom mild potassium deficiency (serum K, 3.4 mEq. per liter) developed. Administration of supplemental potassium resulted in increased excretion of sodium and chloride without a significant increase in excretion of potassium. This effect was also produced by chlorothiazide, which also resulted in a change in excretion of water from free water to osmolar water coincident with a rise in the levels of blood urea nitrogen.

clearance changed from free to the osmolar form.

CASE 7 (Kimmelstiel-Wilson syndrome).—A 59-year-old man had had diabetes for 10 years, which was treated with 25 units of protamine zinc insulin daily. He had had bilateral amputation at the midthigh in 1956 for gangrene of the legs. Edema of the face and hands developed in 1957.

On admission, blood pressure was 160/70 mm. Hg, and mild cardiomegaly, ascites, and sacral edema were noted. Hematocrit was 35%; WBC 16,950 (normal differential); urine was acid, with specific gravity 1.016, albumin 2+, numerous WBC, RBC, and coarse granular casts; urine culture negative; blood urea nitrogen 9.8 mg. per 100 ml.; fasting blood sugar 177 mg. per 100 ml.; phenolsulfonphthalein excretion 20% in one hour; serum

protein A/G ratio 1.9:3.9 gm. per 100 ml. before diuresis and 2.74:4.64 gm. per 100 ml. after diuresis. Diabetic glomerulosclerosis was the pathologic diagnosis on renal biopsy.

Oral administration of chlorothiazide, 0.5 gm. twice daily, resulted in loss of edema and ascites.

Comment.—The diuretic effect of chlorothiazide was not compared with other diuretic agents in this patient. The urinary volume was small, but excretion of electrolytes was continuous, with increased clearances for sodium, chloride, osmolar water, and, to less degree, potassium (Fig. 6). This was the only patient in whom the concentration of serum protein increased during administration of chlorothiazide.

CASE 8 (Chronic glomerulonephritis of the nephrotic phase with acute exacerbation of the disease).—A 16-year-old girl had had transient pyuria at 2 and 13 years of age. In May, 1957, the clinical picture of the nephrotic syndrome developed, and the patient was treated with prednisone, 80 mg. daily, with slight benefit.

On admission, she had mild pedal edema, blood pressure of 142/100 mm. Hg, and Cushingoid facies. The hematocrit was 44%; WBC 16,200 (normal differential); urine was acid, with maximal specific gravity 1.012; albumin 2+; sugar negative; occasional white cell and hyaline and granular casts; serum cholesterol 760 mg. per 100 ml.; serum protein A/G ratio 2.24:2.58 gm. per 100 ml. All other laboratory data were normal.

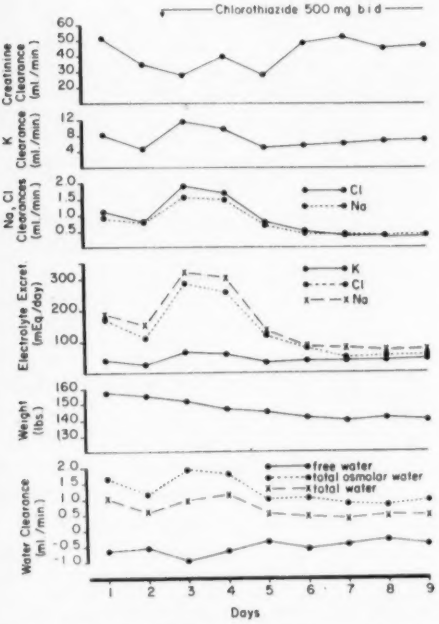

Fig. 6 (Case 7).—Excretory patterns of water and solute in a 59-year-old Negro man with Kimmelstiel-Wilson syndrome. Excretion of sodium, chloride, and osmolar water was significantly increased after administration of chlorothiazide.

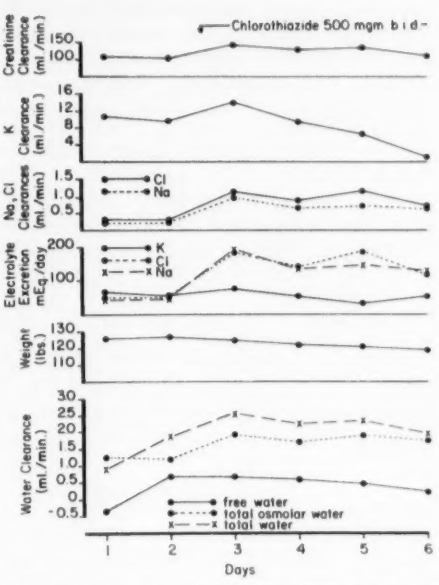

Fig. 7 (Case 8).—Excretory patterns of water and solute in a 16-year-old white girl with chronic nephritis with the nephrotic syndrome. Excretion of sodium, chloride, and free water increased coincident with administration of chlorothiazide. Excretion of potassium did not increase.

Chlorothiazide, 0.5 gm. orally twice daily, produced effective diuresis, but the facial edema disappeared only after prednisone was discontinued. The mild hypertension and urinary abnormalities persisted.

Comment.—This patient had a good diuretic response to chlorothiazide, with increased clearances of sodium, chloride, potassium, and water (Fig. 7).

CASE 9 (Kimmelstiel-Wilson syndrome).—A 24-year-old woman had had diabetes for 10 years, controlled with 40 units of protamine zinc insulin daily. Albuminuria was reported on several occasions over a period of two years, and pedal and periorbital edema developed in November, 1957. She had no significant abnormalities except pretibial edema. The urine showed specific gravity 1.016, albumin, 1+, sugar negative, and 10 to 15 WBC per high-power field; maximal urine concentration 1.016; serum protein A/G ratio 2.49:3.91 gm. per 100 ml.; fasting blood sugar 170 mg.

per 100 ml.; serum cholesterol 280 mg. per 100 ml. Other laboratory data were normal. A clinical diagnosis of diabetic glomerulosclerosis was made.

The edema disappeared after chlorothiazide was given orally, 0.5 gm. twice daily, and the patient lost 10 lb. in four days. Several episodes of insulin shock occurred during chlorothiazide therapy, requiring reduction of the dosage of insulin to 20 units per day. After eight days of treatment with chlorothiazide, the patient began to regain weight without recurrence of the edema. The gain in weight was coincident with the three episodes of insulin shock.

Comment.—Chlorothiazide was an effective diuretic (Fig. 8). The three episodes of insulin shock while the patient was on the same dosage of insulin may have been related to chlorothiazide, since they had not occurred previously. There were not hypokalemic reactions.

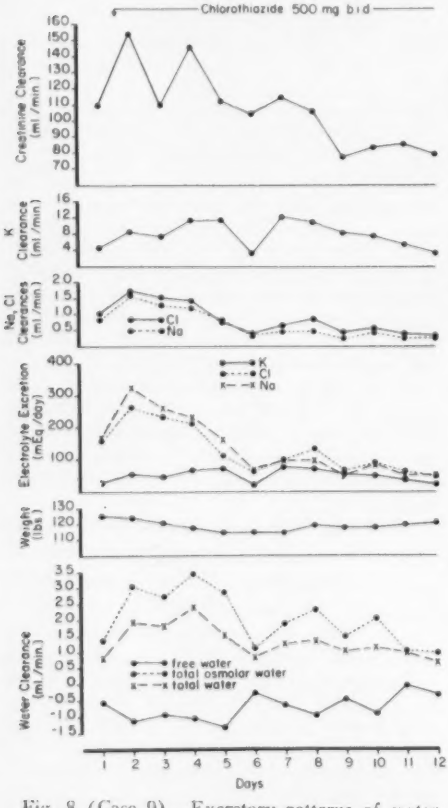

Fig. 8 (Case 9).—Excretory patterns of water and solute in a 24-year-old Negro woman with Kimmelstiel-Wilson syndrome. Chlorothiazide produced loss of weight with increased excretion of sodium, chloride, and osmolar water.

Case 10 (Kimmelstiel-Wilson syndrome).—A 49-year-old man with diabetes of 30 years' duration failed to follow carefully the prescribed diet and insulin and was admitted to the hospital because of nocturnal abdominal cramps, anorexia, and edema. He appeared lethargic and had a blood pressure of 180/140 mm. Hg, diabetic retinopathy, mild epigastric tenderness, and 3+ edema of the legs. Hematocrit was 24%; WBC 15,250 (normal differential); urine was acid, with specific gravity 1.012, albumin 4+, sugar negative; phenolsulfonphthalein excretion 10% in two hours; blood urea nitrogen 72 mg. per 100 ml.; creatinine 7.69 mg. per 100 ml.; serum protein A/G ratio 3.6:2.08 gm. per 100 ml.; fasting blood sugar 190 mg. per 100 ml. Other laboratory data were normal. A clinical diagnosis of diabetic glomerulosclerosis was made.

Treatment with chlorothiazide produced loss of 19 lb. of weight in nine days (Fig. 9). The

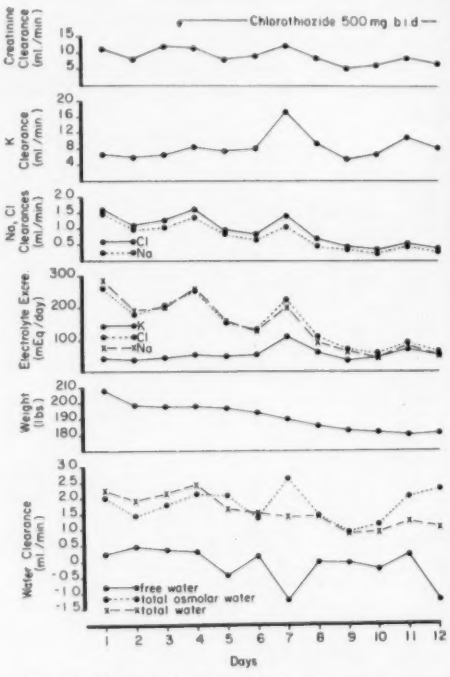

Fig. 9 (Case 10).—Excretory patterns of water and solute in a 49-year-old Negro man with Kimmelstiel-Wilson syndrome who progressively lost weight while receiving chlorothiazide, although the increased excretion of sodium and chloride preceded therapy. The level of blood urea nitrogen became elevated coincident with a change of excretion of water from the free to the osmolar form.

patient appeared to be improved, although the BUN increased from 72 to 92 mg. per 100 ml. without change in blood pressure or creatinine clearance.

Comment.—This patient with diabetic nephropathy and edema had a good diuretic response from chlorothiazide therapy. Clearance studies showed that an initial free water clearance reverted to an osmolar water clearance coincident with chlorothiazide therapy and the rise in BUN, as occurred in Case 6.

General Results and Comments

Chlorothiazide proved to be an effective diuretic agent in these patients with the nephrotic syndrome secondary to various types of renal disease.

Effects of Chlorothiazide on Excretion of Solutes and Water in Nine Patients with the Nephrotic Syndrome

	Mean Daily Excretion		Increase of Mean Excretion, %
	Before Chlorothiazide	After Chlorothiazide	
Na, mEq/L.	122	200	64
Cl, mEq/L.	118	188	59
K, mEq/L.	45	58	28
H_2O, ml.	1,947	2,558	31

Electrolyte Excretion.—The Table summarizes the electrolyte excretion for nine of the patients. All had increased excretion of sodium and chloride with little increase in excretion of potassium after oral administration of chlorothiazide. For nine patients studied before and during chlorothiazide therapy, the mean daily excretion of sodium increased from 122 to 200 mEq. per liter; of chloride, from 118 to 188 mEq., and of potassium, from 45 to 58 mEq. The percentage increases in excretion of electrolytes during administration of chlorothiazide (until "dry" body weight was achieved) over the excretion during the control period were 64% of sodium, 59% for chloride, and 28% for potassium.

Plasma Clearances.—The rates of plasma clearance for sodium, chloride, and potassium were higher in all patients during administration of chlorothiazide than were the control values, with occasional exceptions when a mercurial diuretic was used. In most patients (Cases 1, 3, 5, 6, 7, and 8), the percentage peak increase of clearance rates for sodium during administration of chlorothiazide over control values exceeds that of potassium. In Cases 4, 9, and 10 the percentage peak of increase clearance of potassium before and during administration of chlorothiazide actually exceeded that of sodium clearance, although in all patients the total quantity of sodium excreted far exceeded that of potassium. The creatinine clearances of all patients remained essentially unchanged throughout the entire study, indicating no significant change in glomerular filtration produced by chlorothiazide.

Water Clearance.—The average urinary volume before administration of chlorothiazide was 1,947 cc. daily, which increased to 2,558 cc. (31%) during diuresis by chlorothiazide (measured until dry weight was reached). Four patients (Cases 1, 5, 7, and 9) had osmolar clearances of water greater than total water clearance throughout the control and therapeutic periods, having maximal peak clearances of osmolar water simultaneously with the peak clearance of sodium and coincident with administration of chlorothiazide. Although the urinary volumes in these patients increased at the time of administration of chlorothiazide, they lost relatively greater quantities of electrolytes than of water, and the specific gravity of their urine was 1.012 or greater.

Four patients (Cases 3, 4, 6, and 8) had free water diuresis, with peak free water clearances coincident with the onset of administration of chlorothiazide. Two of these had free water diuresis throughout both the control and treatment periods, whereas in one patient (Case 8) there was negative free water diuresis, with sudden and continuous positive free water diuresis when administration of chlorothiazide was begun. These patients were, therefore, excreting water in excess of electrolytes and had urine specific gravities less than 1.011.

In Case 3, the free water diuresis was relatively greater during use of the mercurial diuretic, whereas electrolyte excretion was relatively greater during treatment with chlorothiazide.

Two patients (Cases 6 and 10) had positive free water diuresis in the control period, with a change to negative free water diuresis during use of chlorothiazide. Both had an increase in blood urea nitrogen coincident with administration of chlorothiazide, without any change in blood pressure or creatinine clearance. The mechanism of this phenomenon remains to be explained.

Blood Pressure.—Four patients had normal arterial blood pressure, which did not change during use of chlorothiazide, and four had mild hypertension (140/90 to 155/100 mm. Hg), which also did not change. Two patients (Cases 3 and 4) had severe hypertension; both were receiving reserpine also, and only one (Case 4) had a decline in blood pressure during use of chlorothiazide.

Potassium Depletion.—Excretion of potassium increased during use of chlorothiazide but was considerably less than for sodium. Reexamination at three months in five patients showed no appreciable depression of serum potassium while they were receiving small daily oral maintenance doses (125 to 500 mg.) of chlorothiazide. During the period of active diuresis, while receiving 0.5 gm. of chlorothiazide twice daily, only 2 of the 10 patients had any decrease in serum potassium concentration, 0.2 mEq. per liter in one and 0.4 mEq. per liter in the other. The remaining eight patients had a slight rise in the level of concentration of serum potassium. The level of potassium in the red cells was not significantly depressed in any of the 10 patients while they were receiving chlorothiazide.

Although renal biopsies have not been repeated, no evidence was found that chlorothiazide had any detrimental effect on the basic renal lesion. This drug only appeared to promote diuresis and to produce dry weight. This, in turn, had considerable psychologic and clinical benefit for the patients, especially those who had been edematous for long periods of time despite other intensive therapy. All edema was eliminated in these 10 patients by the use of chlorothiazide orally, except for the facial edema associated with steroid therapy in 2 patients.

General Comment

These studies reveal the diuretic activity of orally administered chlorothiazide in the nephrotic syndrome due to various renal disease. It approached the effectiveness of the mercurial diuretics when administered parenterally in other types of edema and in general was much more effective than mercurial diuretics in these patients. The detailed mechanism of its action remains obscure. The carbonic anhydrase activity apparently is of minor significance in vivo.[2] The natruretic, chlorouretic, kaluretic, and water-diuretic effects resembled, in general, those of the mercurial diuretics. Its action was prompt and fairly well sustained, and tolerance developed slowly in one patient. It produced less potassium diuresis than sodium, chloride, or water diuresis. Although its toxic effects are yet little known, it was nontoxic even during prolonged administration in these patients. Electrolyte imbalance apparently is its greatest danger, but with careful surveillance these patients did not experience any deleterious effects. As with every new potent drug, many years of experience in many subjects under various circumstances are necessary before its actions and detrimental side-effects become known.

Nevertheless, careful use of chlorothiazide proved to be extremely beneficial in patients reported herein. Physicians have hesitated to use the mercurial diuretics in the presence of renal disease, especially in the presence of acute and subacute inflammation. In the few patients reported here and in several others with the nephrotic syndrome, chlorothiazide proved to be nontoxic but therapeutically effective. Thus far, it has proved effective in maintenance of normal hydration in the presence of severe

hypoproteinemia and hypoalbuminemia. The patients found the drug simple to take, a distinct advantage over periodic needle punctures in the use of mercurial diuretics.

The number of patients studied was small and the follow-up period short, and so any "curative" aspects of the drug in such a variable state as the nephrotic syndrome cannot be evaluated with certainty. Nevertheless, the improvement in the general well-being of some of these patients was impressive. This was particularly true when diligent previous therapy had been ineffective; the patient's legs and body felt heavy; they felt "swollen" and were depressed and discouraged. Prompt diuresis, loss of the heavy, tight, swollen sensation, and development of a more normal-appearing body resulted in a most pleasing reaction of the patient and his doctor. When this was maintained in the presence of severe hypoproteinemia, the results were indeed impressive.

Any conclusion regarding beneficial effects related to the renal tissue itself would be purely conjectural at this time, especially in view of the spontaneous variations of the disease itself and associated therapeutic measures, such as bed rest. However, as measured by the general clinical state of the patient and the urinary findings, two patients were definitely improved beyond merely the loss of edema. Properly integrated with corticotropin (ACTH) or corticosteroids, bed rest, and other general procedures, chlorothiazide may prove to be extremely valuable and reliable. Surely, the drug will not be effective in all patients with the nephrotic syndrome or in all forms of the syndrome, but it is gratifying to have a relatively innocuous, potent oral diuretic that is effective to some extent in the relatively large proportion of patients and even dramatically effective in some.

Others have noted that chlorothiazide reduced the arterial blood pressure in the patients with benign essential hypertension, but it was reduced only in one of our patients who received reserpine concurrently.

Another interesting aspect of these studies is the important physiologic implication of eliminating all edema and maintaining the normal hydrated state in the presence of severe hypoproteinemia. This is further compatible with the extremely dominating role of the kidneys, whether directly or indirectly related, in maintaining the normal state of hydration despite profound imbalance of the Starling factors of oncotic and hydrostatic intra- and extravascular forces. The Starling hypothesis, as generally interpreted, would be incompatible with a normal state of hydration in some of these patients. These studies clearly indicate that the Starling factors are not the only important ones and at times not the dominating ones. The Starling concept needs reevaluation and other factors, including but not only the renal one, require careful study and reconsideration. Furthermore, in view of these observations involving the oncotic forces and others involving the hydrostatic one,[16-20] the Starling concept should be studied in which interotitial chemical, cellular, vascular, endothelial, endocrine, and renal functions are adequately considered.

Summary

In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent. When properly integrated with other well-established clinical procedures, it should prove to be therapeutically beneficial in some patients with the nephrotic syndrome and should at least be given a therapeutic trial. Whether or not it has any "curative" value remains to be determined, but it may prove valuable indirectly by reducing arterial blood pressure and eliminating the water-logged environment of vital cells of the body, including those of the nephron.

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Brucellosis

I. Laboratory-Acquired Acute Infection

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It is unusual to have an opportunity for specific clinical evaluation of patients with infectious disease prior to onset of illness, except in volunteer studies. From 1945 to 1957 sixty cases of acute brucellosis occurred among personnel of a bacteriology laboratory engaged in studies of Brucella melitensis and Brucella suis. These patients had been followed regularly by clinical examination and serological tests before infection occurred. Their known occupational exposure facilitated early diagnosis, hospitalization, and treatment. Many of the infections followed documented laboratory accidents. Most of the patients were observed frequently for one or more years after onset of the acute illness. Analysis of these cases of brucellosis brings out several interesting features of the disease and has made possible appraisal of the incubation period, diagnostic procedures, clinical manifestations, efficacy of chemotherapy, and development of chronic persistent symptoms ("chronic brucellosis").

TABLE 1.—*Initial Data on Sixty Patients with Laboratory-Acquired Brucellosis*

		Patients	
		No.	Total
Age (mean age, 28)	20 yr.	1	
	20-29 yr.	42	
	30-39 yr.	13	
	40-49 yr.	4	
		—	60
Sex	Female	9	
	Male	51	
		—	60
Race	Caucasian	57	
	Negro	2	
	Oriental	1	
		—	60
Bacterial strain	B. suis	31	
	B. melitensis	14	
	Unidentified strain	2	
		—	47 (bacteremia 46; skin ulcer 1)

Clinical Data

Each of the 60 patients was examined at the time of employment, and serological studies and skin tests for brucellosis were performed. Examinations and serological tests were repeated approximately every six months. All patients reported to the same dispensary when they became ill, and all were hospitalized in the same facility for evaluation and treatment.

The background information on these 60 patients is shown in Table 1. The majority were white males between the ages of 20 and 40 years. The diagnosis of acute brucellosis was made by the isolation of Brucella from the blood or marrow aspirate of the acutely ill patient or a rise of serum agglutinins to a titer of 1:100 or greater or both. Seventeen of these cases were the subject of a previous report by Howe et al.[1]

Incubation Period.—In 21 patients a definite laboratory accident was known to have occurred before the development of clinical symptoms. The intervals between accident and onset of illness in these patients are shown in Table 2. Although two patients became ill within a week after presumed ex-

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TABLE 2.—*Interval Between Laboratory Accident and Appearance of Symptoms of Acute Brucellosis*

Interval Between Accident and Symptoms, Wk.	Patients, No.
0-1	2
1-2	2
2-4	6
4-8	7
8-16	3
16-18	1
Total cases analyzed	21
Mean interval, 6 wk.	

posure and one had no symptoms for 18 weeks, the incubation period in most was from 2 to 8 weeks.

Nature of Onset.—There was considerable variation in the mode of onset of illness, ranging from the abrupt development of chill, fever, and prostration to insidious progression of malaise and fatigue over a period of months, occasionally brought to the physician's attention in retrospect. In only 15 patients, however, were symptoms present for more than one week before the illness was severe enough to lead them to seek medical attention.

Symptoms.—The chief complaints of 22 patients on admission to the hospital are presented in Table 3. Malaise and fatigue were the prominent symptoms in one-half of this group. The symptoms during the acute illness in the entire group of 60 cases are listed in order of frequency in Table 4.

Physical Findings.—Abnormal findings on physical examination are listed in Table 4. With the exception of fever, there were few definite findings. Splenomegaly occurred in 10% and hepatomegaly in 13% of patients. Jaundice was not observed.

TABLE 3.—*Chief Complaints of Twenty-Two Patients*

Symptoms	Patients, No.
Malaise & fatigue	11
Fever	10
Headache	8
Chill	4
Myalgia	4
Cough	4
Arthralgia	3
Chest pain	3
Backache	3
Anorexia	3
Pharyngitis	2

TABLE 4.—*Symptoms and Physical Findings During Acute Brucellosis in Sixty Patients*

Symptoms	Patients, No.	Physical Findings	Patients, No.
Headache	50	Fever	54
Fatigue	49	Pharyngitis	19
Feverish	48	Hepatomegaly	8 (4 tender)
Myalgia	42	Rhinitis	7
Chill	34	Splenomegaly	6 (3 tender)
Backache	28	Lung rales	5
Arthralgia	24	Conjunctivitis	1
Nausea	21		
Cough	20		
Pharyngitis	17		
Chilliness	14		
Rhinitis	11		
Vomiting	10		
Diarrhea	7		
Chest pain	5		

Fever.—Maximum temperatures recorded during the acute illness are shown in Table 5. None of eight patients who were afebrile had positive blood cultures. Among 42 patients whose fever lasted seven days or longer, 8 had classical undulating patterns. Twenty-one patients had remittent fever, the temperature rising in the late afternoon or evening and falling somewhat during the morning hours. In 13 patients, fever was intermittent, temperature spiking each evening and dropping to normal in the interim. Of the eight patients who had an undulating fever, seven were bacteremic. Four were infected with B. melitensis and three with B. suis.

TABLE 5.—*Maximum Height of Fever in Acute Brucellosis*

Maximum Temperature, F	Patients, No.
98-99.9	7
100-100.9	7
101-101.9	8
102-102.9	10
103-103.9	9
104-104.9	14
105-106	5
Total	60

TABLE 6.—*Total Blood Leukocyte Count in Acute Brucellosis in Fifty-Eight Patients*

Leukocyte Count	Patients, No.
Normal (5,000-10,000) *	20
Leukopenia (2,000-5,000) †	21
Leukocytosis (10,000-20,000) ‡	22
Leukopenia and leukocytosis §	5

* Leukocyte count normal throughout illness.
† Leukopenia at some time during illness.
‡ Leukocytosis at some time during illness.
§ Leukocytosis and leukopenia during illness.

Treatment.—Salicylates were administered intermittently to 34 patients. Twelve developed shaking chills shortly after taking the medication.

Laboratory Data

Anemia.—Ten per cent of patients had mild anemia. In only two patients, however, was the hemoglobin below 12 gm. % (10.0 and 11.6 gm. %).

Leukocytes.—In 20 patients, the peripheral leukocyte count remained normal throughout the illness (Table 6). Twenty-one were leukopenic at some time, but the white cell count fell below 3,000 in only three cases. Twenty-two patients had leukocytosis, the counts being over 14,000 in five and 19,200 in one. These elevated counts usually dropped to normal within a few days, and five patients with initial leukocytosis subsequently became leukopenic.

TABLE 7.—*Differential Leukocyte Count in Acute Brucellosis*

Differential Leukocyte Ct.	Patients, No.	
	Early in Illness	Late in Illness
Normal *	22	4
Neutrophilia	5	1
Lymphocytosis	25	49
Monocytosis	5	14
Eosinophilia	2	5
	—	—
Total	59	56

* Normal=neutrophils, 50%-75%; lymphocytes, 25%-35%; monocytes, 3%-7%; eosinophils, 1%-3%; basophils, 0%-1%.

TABLE 8.—*Erythrocyte Sedimentation Rate in Acute Brucellosis*

E. S. R., Mm/Hr.	Early in Illness		Middle of Illness		Late in Illness	
	No.	%	No.	%	No.	%
0-10	18	31	1		23	42
10-20	17	30	8	26	16	33
21-30	12	20	7	22	12	22
31-40	3		8	26	1	
41-50	7		2		2	
51-60	1		2		1	
61	0		3		0	

Differential Count.—Among 59 patients who had differential leukocyte counts performed early in the course of illness, these were normal in 24 (Table 7). Five patients had neutrophilia; twenty-five showed lymphocytosis, and monocytosis was present in five. Later during their illness 49 of 56 patients studied had lymphocytosis; 14, monocytosis, and only 1, neutrophilia. Although an initial leukocytosis was found in one-third of the patients, true neutrophilia was present in five.

Erythrocyte Sedimentation Rate (Table 8).—Although erythrocyte sedimentation rates were normal in the early stage of illness in nearly one-third of the patients, almost all finally showed elevations before subsidence of symptoms.

Urine.—Urinalysis revealed few abnormalities. Initial examination showed small amounts of protein in eight patients, micro-

TABLE 9.—*Blood Chemical Studies of Hepatic Function in Acute Brucellosis*

Chemical Analysis	Patients, No.
Cephalin flucculation	9
Positive (+ to ++++)	8
Negative	1
Thymol turbidity	8
2-6	3
6-10	5
Sulfobromophthalein (Bromsulphalein) retention, 30 min.	6
0%-5%	3
5%-10%	3
Serum bilirubin, total	7
Normal	4
1.5-2.5	3
Serum protein, A/G	5
Normal	5

scopic pyuria in seven, microscopic hematuria in three, and cylindruria in two. Attempts to culture Brucella from the urine of several patients were unsuccessful. Proteinuria, hematuria, and pyuria during the course of treatment were almost invariably associated with the administration of sulfadiazine. Bilirubin was detected in the urine of two patients without clinical jaundice.

Liver-Function Studies.—In 11 patients, one or more tests of liver function were carried out. The results of these tests are shown in Table 9. About one-half of these patients showed some abnormality, but none developed clinical evidence of significant hepatic dysfunction.

Roentgenograms.—Chest x-rays of 42 patients were normal. A right midlung infiltrate in one patient with B. suis bacteremia was associated with the presence of Type 29 pneumococci in the sputum. In another patient a left lower lobe infiltrate and bilateral small pleural effusions were found in a clinical setting compatible with pulmonary infarction. Roentgenographic study of bones and joints in several patients demonstrated no abnormalities.

Miscellaneous Studies.—Electrocardiograms were taken in six cases. All were within normal limits. Lumbar puncture in one patient revealed normal cerebrospinal fluid.

Blood Cultures.—In 46 of the 60 patients, one or more positive blood cultures were obtained during the acute illness. B. suis was isolated in 30 cases and B. melitensis in 14. The species was not determined in the two remaining patients.

In obtaining blood cultures, 20 ml. of venous blood was removed by aseptic technique. Five milliliters was put into a bottle containing heparin, and one milliliter aliquots were injected intraperitoneally or subcutaneously into guinea pigs. Five milliliter samples were inoculated directly into three flasks of modified Castenada medium, and the cultures were examined daily for 30 days. Guinea pigs were killed after 30 days; heart blood was cultured and examined for Brucella agglutinins. All gross pathologic lesions of viscera or lymph nodes were excised, minced, mixed with saline, and cultured.

Bone Marrow Cultures.—The bone marrow was cultured in 11 cases. In six patients who had positive blood cultures, the marrow culture was positive, and in four patients without detectable bacteremia, mar-

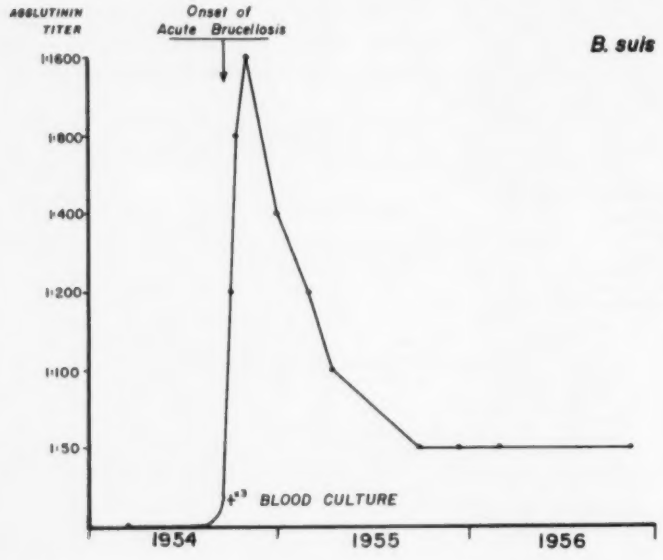

Fig. 1.—Serological response representative of the type pattern observed in 38% of patients followed for one year or longer.

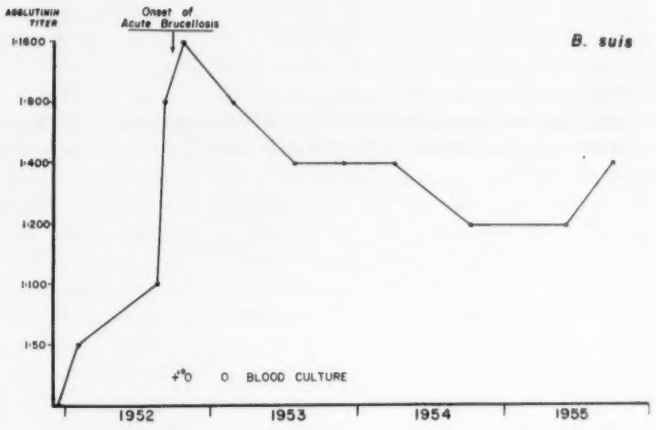

Fig. 2.—Serological response representative of the type pattern observed in 28% of patients followed for one year or longer.

row cultures were negative. In the only patient with bacteremia who had a negative bone marrow culture, the marrow aspiration was carried out after the institution of tetracycline and streptomycin therapy.

Serological Data.—Serum agglutinin titers were determined for all patients before onset of disease, several times during illness and convalescence, and, in the majority, during follow-up periods of more than one year. Agglutination tests were performed by a serial dilution tube method with use of Brucella abortus antigen Strain 1119-3. Simultaneous determinations of Pasteurella tularensis agglutinins were performed in most instances.

Only 39 cases, where information was available for a period greater than one year after onset of illness, were considered in analysis of the character of the serologic response. These patients could be divided into three distinct groups on the basis of the course of their agglutinin titers:

1. A response representative of this group is shown in Figure 1. Here the agglutinin titer rose sharply during the acute infection and gradually fell to less than 1:100 during the next several months. Fifteen of the thirty-nine cases displayed this pattern. Of 10 cases in this group with bacteremia, 8 were due to B. suis and two to B. melitensis.

2. The second type of serological pattern is illustrated in Figure 2. A similar initial rise occurred, but a sustained elevation at or above 1:100 persisted without significant variation during the entire period of follow-up. This pattern occurred in 11 patients, 7 of whom had demonstrated bacteremia due in each instance to B. suis.

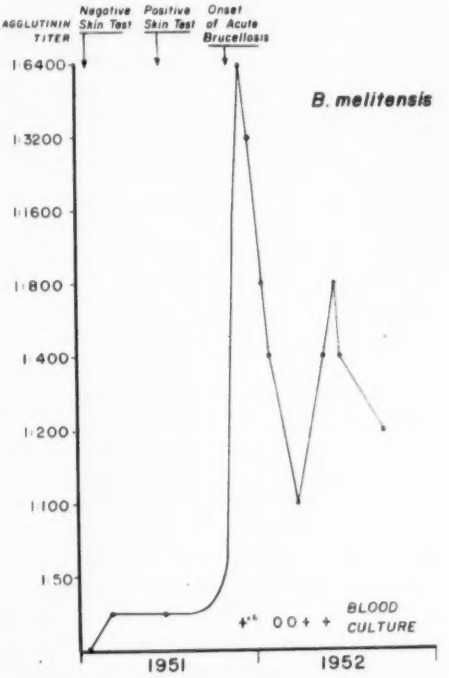

Fig. 3.—Serological response representative of the type pattern observed in 34% of patients followed for one year or longer.

3. An example of the third type of response is seen in Figure 3. The pattern in this group was characterized by one or more secondary rises. The secondary elevations in most instances coincided with recurrences of fever and bacteremia. Bacteremia was demonstrated in 11 of the 13 patients in this group (due to B. suis in 4 and to B. melitensis in 7). Subsequent to the last secondary elevation in this third group the titer gradually fell to a level of less than 1:100 in about one-half of the patients and remained above this level in the rest.

The promptness of the initial rise in agglutinin titer was striking. In only two patients were no agglutinins detectable at the time of onset of symptoms. Antibody levels in both cases subsequently rose to 1:6400. In one case the initial illness was probably β-hemolytic streptococcal pharyngitis, and Brucella bacteremia was not demonstrated until the 20th day of illness. Five patients had initial titers of 1:25 during the early portion of illness, but the remaining fifty-three developed agglutinins in a titer of 1:50 or greater promptly, even when sera were tested on the first day of symptoms. In 11 patients studied within the first three days of illness, agglutinins were already present in a titer of 1:200 or greater. Many of these patients had received injections of Foshay's tularemia vaccine.[2] There was usually no change in the agglutinin titers for P. tularense during acute brucellosis, and when such a change did occur it could be attributed to a recent injection of the vaccine.

Two patients had acute tularemia subsequent to their acute brucellosis, and in neither of these cases was there any rise in the level of Brucella agglutinins concomitant with P. tularense in fection.

Skin Tests.—Intradermal testing with Brucellergen (a suspension of nucleoprotein from Brucella cells) or brucellin was carried out in 56 of the 60 patients prior to onset of illness. Fifteen patients received one or more injections of Brucella vaccines before contracting brucellosis. Usually these injections were not followed by the appearance of agglutinins, and in no case did they lead to the development of a positive skin reaction.

The initial skin test was positive in three patients. In one of these patients the agglutinin titer was negative prior to the acute illness; in a second, 1:25, and in a third, 1:100. Three other patients who had negative tests when first tested had developed positive skin reactions 2, 5, and 22 months, respectively, before the occurrence of acute illness with bacteremia.

Thirteen patients with negative skin tests prior to becoming ill were tested again at intervals varying from the day of onset to 14 months after recovery from acute brucellosis, and in all the reaction had become positive.

Among the 56 patients who had been skin-tested, the majority demonstrated no subsequent change in the agglutinin titer that could be attributed to the skin-testing. In four cases, however, this test may have been responsible for a twofold elevation in titer; in three cases, a fourfold elevation, and in one case, an eightfold elevation. A positive skin test was no more likely to be followed by an elevation than a negative reaction. In no case did the use of the skin test cause confusion in diagnosis.

An interesting reaction encountered in seven patients, previously described by Howe et al.,[1] was the appearance during the acute illness of erythema and induration at the site of a skin test performed months previously. In one patient, this reaction developed on the 4th day of illness; in four, between the 17th and 30th days; in one, on the 50th day, and in one, not until the 73d day after onset of illness. In one case, the reaction appeared on the 17th day and was so severe that an indolent ulceration developed, requiring over three months to heal.

Complications

Left *epididymitis*, lasting seven days, occurred during the sixth week of illness in a patient with B. suis infection. A few days later, a small mass appeared transiently in the region of the left breast. Another pa-

TABLE 10.—*Treatment in Acute Brucellosis in Sixty Patients*

Treatment	Patients, No.
None	12
Sulfonamide	13
Tetracycline	6
Streptomycin	2
Streptomycin & tetracycline	22
Streptomycin & sulfonamide	2
Streptomycim, tetracycline, & sulfonamide	3
Total	60

TABLE 11.—*Duration of Fever in Relation to Therapy of Acute Brucellosis* *

Therapy	Patients, No.	Mean Duration of Fever After Starting Therapy, Days
None	9	3.0 (total duration of
Sulfadiazine	12	4.5 fever in
Sulfadiazine & streptomycin	13	3.7 hospital)
Tetracycline	6	2.2
Tetracycline & streptomycin	12	3
Streptomycin	1	10
Sulfadiazine & tetracycline & streptomycin	1	3

* 8 patients had no fever at anytime; 4 patients had no fever at onset of treatment; 1 patient had drug fever (streptomycin); 1 patient had concomittant pneumococcal pneumonia.

tient with serologically diagnosed brucellosis developed *swelling of the left breast* in the fifth week of illness. Biopsy revealed only gynecomastia, and cultures were negative. *Tender swelling of the left testicle* appeared in a patient with a B. melitensis infection nine months after he first became ill. Persistent sternomanubrial tenderness associated with *chronic synovitis* of the sternomanubrial joint occurred in a patient who had had both acute brucellosis (B. suis) and tularemia. *Bilateral indolent malleolar ulcers* developed 11 months after onset of illness in another patient and were the only source from which the organism (B. suis) was isolated.

Other disease processes occurring with acute brucellosis were not common. Coexistent pneumococcal pneumonia and acute brucellosis were found in one person. *Pulmonary* infarction probably occurred in another. β-Hemolytic streptococci were isolated from the throats of six patients, three of whom had *pharyngitis*.

Therapy

The various chemotherapeutic programs employed in the patients of this study are listed in Table 10. Twelve received no specific treatment. Adrenal cortical extract was given to one patient but produced no clear-cut effect on her clinical course. Evaluation of the various therapeutic regimens was difficult because of the vague nature of many of the symptoms of acute brucellosis and the paucity of physical abnormalities. Duration of illness seemed an unsatisfactory criterion of therapeutic effectiveness because of the lack of a clear end-point. The efficacy of treatment was assessed in four ways: (1) *duration of fever* after institution of therapy; (2) effectiveness of the agent in the *elimination of bacteremia*; (3) *prevention of recurrent illness*, and (4) *prevention of chronic symptoms*.

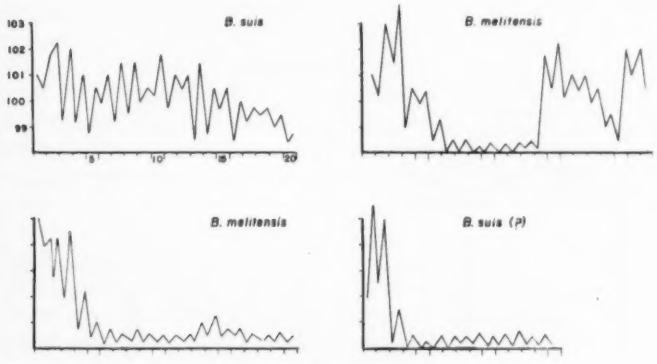

Fig. 4. — Temperature curves of four representative patients who received no treatment for acute brucellosis.

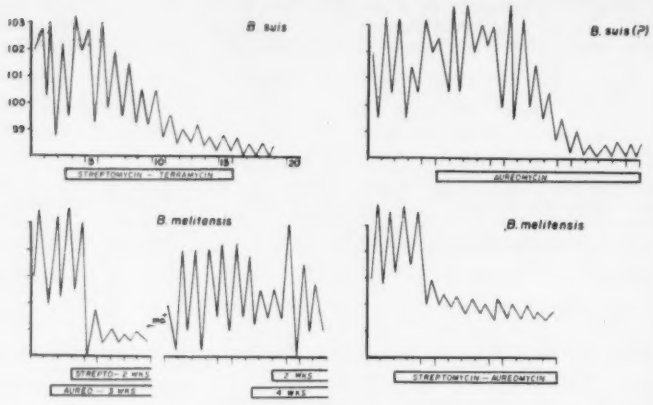

Fig. 5. — Temperature curves of four representative patients who received tetracycline and/or streptomycin for acute brucellosis.

The apparent lack of effect of any agent or combination of agents on *duration of fever* is shown in Table 11. Fever persisted for an average of slightly over three days no matter what program was employed, and the duration of fever in patients receiving no chemotherapy at all was similar.

The difficulty in demonstrating any effect of these agents on the febrile course of acute brucellosis is further illustrated in Figures 4 and 5. In Figure 4 are shown the temperature curves of four patients who received no chemotherapy. Abrupt defervescence, gradual defervescence, and undulating fever are all represented. In Figure 5, similar temperature curves are depicted in patients given streptomycin, tetracycline, or a combination of these agents.

The *incidence of bacteremia* during therapy with each regimen is shown in Table 12. Although combined treatment with streptomycin and a tetracycline did not always abolish bacteremia immediately, the incidence of bacteremia during therapy with these drugs was substantially less than in patients receiving sulfadiazine.

TABLE 12.—*Effect of Treatment upon Bacteremia in Acute Brucellosis*

Treatment	Patients, No. Persistent Bacteremia */ Total with Bacteremia
Sulfonamides	5/9 B. melitensis -3/4 B. suis -2/5
Streptomycin	0/2
Tetracycline	1/3
Streptomycin & tetracycline	3/19 B. melitensis-1/5 B. suis -2/14

* Number of patients with persistence of bacteremia after 48 hr. of treatment.

TABLE 13.—*Twenty-Two Patients with Serological and Bacteriological Recurrences*

	Total Patients with Recurrences	Recurrences No/ Total Cases	Recurrences %
Serological recurrence	7	22/60	37
Bacteriological & serological recurrence	15		
B. melitensis	9	9/14	64
B. suis	6	6/13	19
Treatment of original illness			
None	3	3/12	25
Sulfadiazine	7	7/13	54
Streptomycin & tetracycline	7	7/22	32
Tetracycline	3	3/6	50
Sulfadiazine & streptomycin	2	2/2	100
Total	22		

Twenty-two patients had recurrent acute illness. Fifteen had associated bacteremia, and all showed a secondary elevation in the agglutinin titer. Data concerning these patients are given in Table 13. The number of patients receiving each of the various regimens in treatment of the original illness is not large enough to permit definite conclusions, but it is of interest that the recurrence rate did not fall below 32% with any

TABLE 14.—*Effect of Treatment upon Development of "Chronic Brucellosis"*

Treatment	"Chronic Brucellosis"/ Total Cases, No.
None	6/12
Sulfonamide	2/13
Streptomycin & tetracycline	10/22
Tetracycline	3/6
Streptomycin & sulfonamide	1/2
Miscellaneous	2/5
	24/60

program of therapy. The lower recurrence rate in untreated patients may in part be related to the mild character of the initial illness in most of these patients.

Twenty-four patients complained of persistent symptoms for more than six months after the onset of illness. In Table 14 is shown the distribution of these patients among the various regimens of treatment of the acute illness. The number in the various groups is again too small to draw conclusions about the relative effectiveness of the agents, but it is readily apparent that none completely prevented "chronic brucellosis."

It can be said that none of the drugs employed produced a definite effect on the duration of fever, recurrence of acute illness, or development of chronic symptoms. Streptomycin and tetracycline in combination were more successful than sulfadiazine in abolishing bacteremia during the *period of treatment*, but they were not effective in preventing recurrence of bacteremia. It may be concluded that none of these treatment programs yielded consistently satisfactory results in the treatment of acute brucellosis. The rarity of granulomatous and suppurative complications in the 60 cases, however, does not allow an analysis of treatment on this feature of brucellosis.

Complications of chemotherapy were infrequent. *Drug fever* due to streptomycin developed in one case. Microscopic hematuria occurred in five patients receiving sulfadiazine. One patient received 24 gm. of chlortetracycline during the first 48 hours and 8 gm. per day for 11 days and developed *nausea and vomiting and a ravenous appetite*. One patient had recurrence of fever and bacteremia immediately after receiving treatment with tetracycline and streptomycin (Fig. 6).

Recurrent Acute Illness

Twenty-two of the sixty patients had recurrence of acute illness, associated with

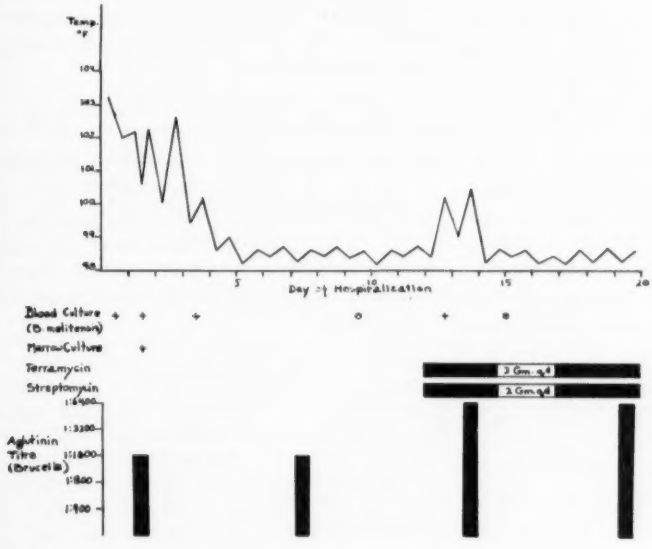

Fig. 6.—Recurrence of fever and bacteremia in a patient with acute brucellosis immediately after starting tetracycline and streptomycin treatment (Herxheimer reaction).

bacteremia in fifteen and with a secondary elevation of the agglutinin titer in all. In general, the symptoms and physical findings associated with recurrences were the same as seen during the initial illness, although recurrent episodes were often milder. The interval between seeming recovery from acute brucellosis and recurrence varied from 2 weeks to 11 months, and, while this interval was often symptom-free, it was sometimes characterized by varying degrees of fatigue and malaise. B. melitensis infections were followed by recurrences with bacteremia in nine cases, and illness with bacteremia due to B. suis recurred in six patients (Table 13). The rate of recurrence with bacteremia was therefore 64% in B. melitensis infections and 19% in B. suis infections. Two patients with B. suis infections had two separate recurrences with bacteremia, and one patient with a B. melitensis infection had three such recurrences. None of the chemotherapeutic agents employed was consistently effective in preventing recurrent acute illness, as mentioned before.

"Chronic Brucellosis"

A major difficulty in the study of "chronic brucellosis" has been the lack of well-defined objective diagnostic criteria. In this study we have classified as having "chronic brucellosis" all patients with complaints of malaise, fatigue, myalgia, arthralgia, backache, or feverishness for a period of one year or longer beyond the acute illness, unassociated with bacteremia, changing serological titer, or physical abnormalities. This was done not with the opinion that all such patients were afflicted with "chronic brucellosis" but simply to facilitate analysis of the chronic symptom state, whatever it might represent. This symptom state is distinct from recurrent acute illness with bacteremia or with secondary rise in agglutinin titer.

Among the 60 patients in this study, 24 were diagnosed as having "chronic brucellosis." Of 14 in whom bacteremia was demonstrated during the acute illness, 10 had B. suis infection and four had infection due to B. melitensis conforming to the proportion of infections due to each organism in the entire group of 60 patients. There seemed to be no greater tendency for chronic symptoms to follow infection by one species than the other.

For 19 of the 24 cases serological data were available for periods longer than one year. After subsidence of acute symptoms, eight patients demonstrated a gradual fall in titer to below 1:100, four showed persistent elevation of titer at or above 1:100, and seven had secondary elevations in titer. This distribution of serological patterns corresponds to that found in all of the 39 cases for which long-term data were available, thus revealing no characteristic serological pattern in association with the "chronic brucellosis." Persistent elevation of titer at or above 1:100 was as likely to be found in a patient who had recovered completely as in a patient with persistent chronic symptoms.

In Table 14 are shown the distributions of the various chemotherapeutic regimens among the entire group of 60 cases as compared with the distribution of these same regimens among the 24 patients with chronic complaints. There was no single program which made the development of chronic symptoms less likely.

It must be emphasized that this analysis of "chronic brucellosis" does not include persons with chronic granulomatous complications. It is apparent, however, that it was not possible to correlate "chronic brucellosis" with strain of organism or type of serological pattern and that no chemotherapeutic agent prevented the emergence of such a state.

Report of Cases

Recurrent Acute Brucellosis; Subsequent Tularemia.—A 45-year-old acutely ill Negro man was admitted, on Nov. 20, 1950, with a five-day history of chilliness, headache, and myalgia. As shown in Figure 7, his hospital course was characterized by remittent fever, with temperature as high as

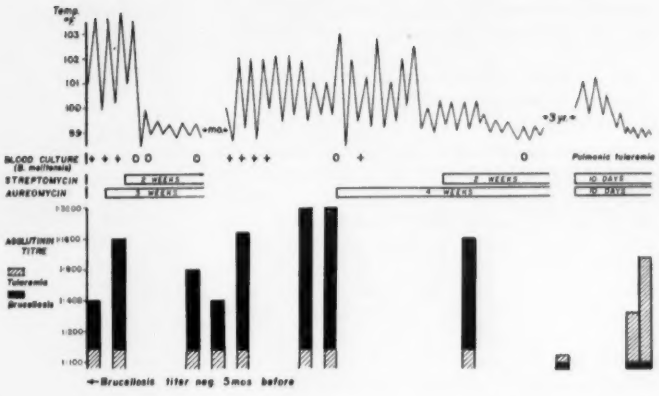

Fig. 7.—A patient who developed acute tularemia three years after recovery from acute brucellosis.

104 F, for the first four days, and the rise of agglutinin titer with the acute illness is plotted. Blood cultures revealed B. melitensis. A 21-day course of chlortetracycline (3 gm. per day) was administered, and dihydrostreptomycin (2 gm. per day) was given for 12 days. Although afebrile after the fourth day, the patient continued to complain of low back pain. His Brucella agglutinin titer, previously negative, rose to 1:1600. Leukopenia, with counts as low as 1,900 per milliliter, was observed early in the illness, and the sedimentation rate rose to 45 mm. per hour. Other laboratory studies were normal.

After discharge, the patient felt well except for occasional fatigue and backache. On Jan. 3, 1951, he complained of increasing fatigue, and a blood culture at that time was again positive for B. melitensis. Five or six cultures during the next 11 days were also positive, and during this time headache, backache, and a dry cough developed. On Jan. 12 he was admitted to the hospital, and for the following 20 days remittent fever, with temperature up to 103 F, was present, pyrexia disappearing on the 10th day of a second course of chlortetracycline and streptomycin. Again there were no striking physical findings, but leukopenia was present.

After his second hospitalization, the patient continued to complain intermittently of marked fatigue. In August, 1951, he developed transient tender swelling of the left testicle. He continued to complain of easy fatigability and low back pain, and he was believed to have "chronic brucellosis."

In November, 1954, the patient contracted tularemic pneumonia, and his P. tularense agglutinin titer rose to 1:1280. There was no change in the level of Brucella agglutinins. The patient had received many injections of Foshay vaccine prior to contracting tularemia.

Acute Brucellosis with Coexistent Pneumococcal Pneumonia.—A 28-year-old white man entered the hospital on Dec. 18, 1948, after three days of anorexia, headache, myalgia, productive cough, and diarrhea. He had been involved in a laboratory accident with B. suis one month previously. His temperature on admission was 102 F. Rales were heard over the right anterior chest. Roentgenogram revealed an infiltrate in the right midlung field. Type 29 pneumococci were isolated from the sputum. Penicillin therapy (300,000 units per day) was instituted, and there was rapid clearing of the infiltrate. Spiking fever, with temperature as high as 104.2 F, continued (Fig. 8), however, and on the seventh hospital day it was found that the original blood cultures contained B. suis. Sputum culture for Brucella was negative. Chlortetracycline (4 gm. per day) was begun, but the patient remained febrile for four more days. Brucella agglutinins appeared in a maximum titer of 1:3200. The white blood cell count was 10,200 per milliliter on the day of admission but normal thereafter.

Six weeks after onset of his initial illness, the patient developed a recurrence, with bacteremia and

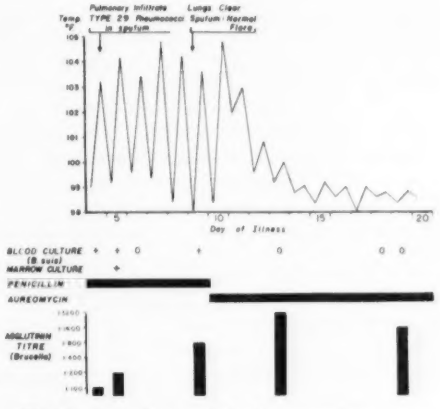

Fig. 8.—A patient who had pneumococcus pneumonia and acute brucellosis concomittantly.

fever (temperature up to 103 F), cervical lymphadenopathy, and mild hepatomegaly. Administration of acetylsalicylic acid on a single occasion was followed within three hours by a shaking chill. Chlortetracycline was administered again for a two-week period.

The patient continued to complain of fatigue and malaise, and 14 weeks after his first symptoms he had another recurrence of acute illness with bacteremia and was given chlortetracycline for three weeks. He continued, however, to complain of recurrent malaise, weakness, and feverishness. The hepatomegaly persisted, but blood cultures were negative. The patient left the area in 1952, and no further information is available.

Symmetrical Chronic Ulcers of the Feet Due to B. Suis.—A 49-year-old white man entered the hospital on March 5, 1952. He gave a history of a chronic cough and recurrent febrile episodes, and on at least two occasions in the preceding 12 years he had had pneumonia. Brucella skin tests and agglutinins had been negative on numerous occasions. Two days before admission, the patient developed chills, fever, headache, sore throat, cough, and myalgia. His temperature was 101 F on admission, but defervescence occurred within 24 hours. Physical examination revealed pharyngeal injection and bilateral pulmonary basilar rales. He received no specific therapy and was asymptomatic by the third day. A chest film on the eighth day, however, revealed a small infiltrate in the right upper lung field, and he was given dihydrostreptomycin (2 gm. per day) for 2 weeks and oxytetracycline (2 gm. per day) for 25 days. The infiltrate gradually resolved over this period. Brucella agglutinins were present in a titer of 1:800 on admission and remained at this level over the next month. Blood cultures were sterile. Sputum cultures revealed only normal flora.

During the following 10 months, the patient had recurrent episodes of malaise, feverishness, and anorexia. On Feb. 12, 1953, he had a shaking chill with malaise and headache. The dorsa of his feet began to itch, and vesicles appeared. These developed over the next few days into bilateral symmetrical ulcers in the regions of the medial malleoli (Fig. 9). He was readmitted to the hospital and for several days thereafter had a low-grade fever. Mild hepatomegaly was present. X-ray of the chest was normal, as were films of the ankles. Blood cultures were again sterile, but B. suis was cultured from each ulcer on five separate occasions. There was a secondary elevation of the Brucella agglutinin titer from 1:100 to 1:400. The patient was treated again with oxytetracycline (2 gm. per day) and dihydrostreptomycin (2 gm. per day), and the ulcers were treated by enzymatic debridement. Healing of the ulcers was not complete for four months, although the patient seemed otherwise well.

Fig. 9.—Symmetrical ulcers of the ankles due to B. suis in a patient with acute brucellosis.

Over the ensuing four years, recurrent episodes of fatigue and myalgia have continued, and he has had brief courses of tetracycline therapy. Blood cultures have never been positive. The agglutinin titer had not fallen below 1:100 through April, 1956.

Induction of Chill and Hectic Fever in Acute Brucellosis by Sporadic Salicylate Administration; Recurrent Bacteremia Without Symptoms.—A 40-year-old white man entered the hospital on Aug. 23, 1950. He had worked with Brucella at various times since 1934, and his skin test had been positive. His agglutinin titer in February, 1950, however, was only 1:25. He was unaware of previous symptomatic acute brucellosis.

On Aug. 12, 1950, the patient developed headache, myalgia, and fever, which persisted. For five days after admission to the hospital he had a hectic fever with temperature as high as 104.3 F. Tender lymph nodes were present in the left axilla, and there was tender hepatomegaly. Precipitous fall in temperature and shaking chills followed administration of single doses of acetylsalicylic acid on six occasions. Two blood cultures were positive for B. melitensis, and the agglutinin titer rose to 1:400. A four-week course of chloramphenicol (3 gm. per day) and a two-week course of streptomycin (2 gm. per day) were given. The patient became afebrile on the sixth hospital day and felt well thereafter.

On Oct. 24, 1950, he was found to have a secondary rise in the Brucella titer to 1:800 and a positive blood culture, although a number of

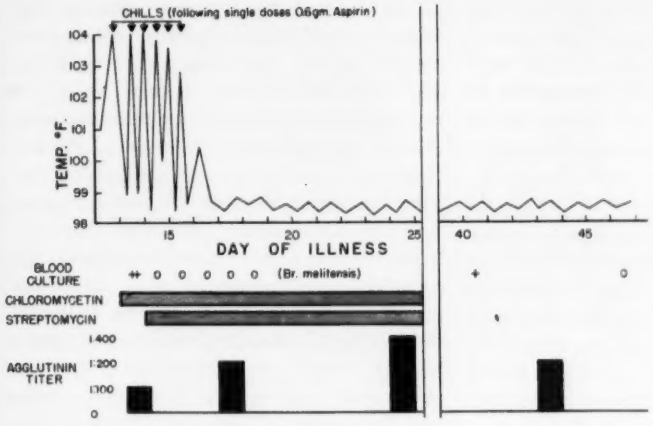

Fig. 10.—A patient who developed hectic temperature curve and repeated chills attributable to administration of an antipyretic. Recurrent bacteremia without symptoms.

interim and subsequent cultures were negative. No symptoms were present at the time of the positive culture (Fig. 10).

Comment

There were a few differences between the disease caused by B. suis or B. melitensis which could be detected in these patients. Suppurative and granulomatous complications occurred with B. suis infection only, and these were characterized by indolent ulcers of the ankles and granulomatous synovitis of the sternomanubrial joint. Undulating fever or recurrent acute illness was commoner in B. melitensis infections, and the single Herxheimer reaction occurred in a patient with infection by this species. Leukocytosis and peripheral neuritis have been reported to occur more frequently in B. melitensis infections,[3,4,8] but leukocytosis occurred early in the course of the disease in most of the patients studied, whether infection was due to B. suis or B. melitensis, and peripheral neuritis was not seen at all. B. abortus probably produces a milder illness than either B. suis or B. melitensis, but this could not be evaluated.

Many of the infections in these patients occurred following recognized laboratory accidents, such as spillage or breakage of a culture flask. It was impossible to be certain of the route by which infection was produced, but in several instances it seemed likely that inhalation of the Brucella was responsible.[5] The variation of the incubation period in these persons was typical of that described before,[3,5,6] and it may be partly attributable to the vague manifestations observed during the acute disease, making it difficult, at times, to define the time of onset of symptoms. Development of a positive skin test 2 to 22 months prior to onset of the acute illness in three patients suggests that subclinical infection may occasionally account for apparent prolongation of the incubation period. The onset of illness has been reported[3] to be insidious in about one-half of patients with infection by B. abortus, whereas in the patients studied here less than one-fourth had symptoms for more than one week before seeking medical attention. This may be more a reflection of the program of medical care provided than any greater severity of illness, however.

The most prominent symptoms in these cases of brucellosis were similar to those described in other series,[3] and fever was the single physical abnormality observed with some regularity. The paucity of objective signs in acute brucellosis resembled that reported by others.[3,6]

Although *undulating fever* occurred in one-third of the patients with B. melitensis infection,[7] it was also observed in 10% of infections due to B. suis. The reason for propensity of B. melitensis infection to pro-

duce acute febrile recurrences with an undulating course is not known. Induction of repeated chills in brucellosis by the administration of antipyretics is comparable to the development of chills in typhoid fever under similar circumstances. Otherwise, more than one chill was unusual, as described before by Huddleson.[6]

The high incidence of leukocytosis in the cases presented here is probably explained by the fact that most patients were seen early in their illness. Almost all developed leukopenia, however, within the first few days of observation. Even in the presence of leukocytosis there was usually lymphocytosis.[4] The erythrocyte sedimentation rate is frequently said to be normal in acute brucellosis, but it was abnormally increased at sometime during the illness in most of our cases.

The intracellular localization of Brucella[8,9] is very likely responsible for its insusceptibility to the action of specific antibody and chemotherapeutic agents. Persistence of bacteremia in the patient with high agglutinin titer or after institution of treatment with bacteriostatic and bacteriocidal drugs may be accounted for by the engulfment of this micro-organism by leukocytes and macrophages. Similar examples of the persistence of bacteremia or infection are seen in other infections by Gram-negative bacilli, and recently such persistence has been shown to be responsible for the bacteremia in staphylococcal infection of rabbits.[10]

The availability of preinfection serum agglutinin titers for brucellosis in these patients made it possible to attach additional significance to this serological test for diagnostic purposes. Where a negative titer was previously known, the finding of agglutinins in a titer of 1:50 or above was almost pathognomonic of brucellosis. In no patient was the agglutinin titer negative, even when it was determined on the day of onset of symptoms. This corresponds with Spink's[3] observations that bacteremia is rarely demonstrated in the absence of serum agglutinins. The elevated serum antibody titer at the onset of symptoms of illness supports the concept that hypersensitivity may be an important mechanism of host injury in brucellosis, indicating an association between altered host reactivity and onset of disease. Secondary elevations of agglutinin titer were the rule in cases of undulating or recurrent acute illness. The fact that antibiotic treatment of acute brucellosis, although begun promptly after onset of symptoms, failed to influence the course of the serological titer after recovery is probably attributable to the prolonged antigenic stimulation during the incubation period and early in the illness, prior to institution of treatment. Whether or not persistence of Brucella in the reticuloendothelial cells provides a continuing source of antigen to account for the prolonged elevation of agglutinin titer above 1:100 in one-third of patients can not be stated at this time. Certainly, there was no relationship, however, between persistently elevated titer and the development of "chronic brucellosis," which might suggest that persistence of bacteria in the tissues bears no direct association with chronic symptomatic illness in the absence of physical abnormalities.

The lack of an anamnestic rise in agglutinin titer for tularemia during acute brucellosis was somewhat surprising in view of the prevailing opinion on the subject.[3,6,11,12] A cross reaction between the agglutinins formed in brucellosis and tularemia was expected because of the antigenic similarities between Brucella and P. tularensis.[6,12] The patients in this study had been immunized with tularemia (Foshay) vaccine,[2] and so elevations of agglutinin titer were seen to be attributable to this. Two patients who contracted tularemia after recovery from brucellosis, however, had no change in the Brucella titer.

Hypersensitivity to Brucella antigens was uniformly detected by skin test after onset of illness[3,11] and, when determined, was present on the first day of illness. The

implications of hypersensitivity in brucellosis, already alluded to, have been studied extensively by Spink and his associates,[3,13,14] and it has been shown that symptoms of brucellosis can be reproduced in the patient who has a positive skin test but has recovered from the acute disease, by inoculation of the somatic antigen of the micro-organism. Hypersensitivity may be of importance in the pathogenesis of brucellosis, as it is in tuberculosis. Another indication of this is the development of severe inflammation at the site of a previous skin test upon the development of the acute infection.[1]

The infrequency and irregularity of elevation of the Brucella agglutinin titer after skin testing in this study indicates that this method of diagnosing brucellosis, previously suggested by Carpenter and Krakauer,[15,16] is not reliable.

Herxheimer reactions occurring in acute brucellosis after institution of tetracycline therapy [17] may be severe. Reappearance of bacteremia with this reaction in a patient observed here is of interest, although the mechanism involved in this event is unclear. If hypersensitivity is involved in the Herxheimer reaction by liberation of bacterial antigen after beginning antibacterial therapy, this might be associated with disintegration of sensitized cells harboring the micro-organism, thereby producing recurrence of bacteremia.

Pneumonitis in brucellosis has been described,[23,24] but there is some question as to whether or not this always represents involvement of the lung by Brucella. It has been suggested that pulmonary involvement may more often be attributable to invasion by other pathogens.[6] It is of interest, in this regard, that the only instance of pneumonia in the patients studied here was probably due to the pneumococcus.

The failure of tetracycline prophylaxis (3 gm. per day for 7 days), given to one patient after exposure, to prevent development of acute brucellosis is analogous to the failure of chloramphenicol prophylaxis in tularemia, reported by McCrumb, Snyder, and Woodward.[18] Tetracycline is a bacteriostatic drug for Brucella, and it is very likely that a bacteriolytic drug, such as streptomycin, may be a more effective prophylactic agent.

Most of the manifestations of acute brucellosis are sufficiently indistinct and variable to make it very difficult to assess the effectiveness of any therapeutic agent.[3] In many instances the disease is self-limited and there may be abrupt or gradual recovery. An attempt was made, however, to determine whether or not either of the therapeutic regimens employed notably changed the course of infection, and no agent consistently shortened the febrile period, prevented the development of "chronic brucellosis," or prevented acute recurrences of illness with bacteremia. It is possible that treatment with streptomycin and tetracycline might reduce the incidence of suppurative and granulomatous complications, but this could not be determined. The more prompt termination of bacteremia in patients treated with these drugs, however, may be an indication of a protective influence of streptomycin and tetracycline therapy in acute brucellosis.

We had no experience with the use of adrenocortical steroids in suppressing the manifestations of acute brucellosis; however, others have shown that these hormones can produce marked amelioration of fever and symptoms without deleterious effects.[19,21] This is in contradistinction to the effect of cortisone upon experimental acute Brucella infection of mice, where a benign disease may be converted into a fulminant process.[19]

Spink [22] has delineated very clearly the problem of "chronic brucellosis" and has defined a group of patients in whom there were no objective features which served to identify their illness. These are patients who have symptoms of fatigability, vague aches, and depression persisting for longer than one year after acute brucellosis, in the absence of positive physical findings. A rather high incidence of this illness occurred among the patients studied here (40%),

and no correlation was detected between the development of the chronic illness and the nature of their acute infection, the behavior of the agglutinin titer, or the mode of treatment of the acute infection. A further investigation of the persons having "chronic brucellosis" was undertaken and is reported in Part II of this series.

Summary

Sixty cases of acute brucellosis are described. These infections were caused by exposure to Brucella suis and Brucella melitensis in a bacteriological laboratory. The clinical and laboratory features of the disease are defined.

The incubation period of infection was usually four to eight weeks. A paucity of physical findings was detected in the acutely ill patient, fever being the most frequent observation. Serological studies performed *before, during,* and *after* the infection illustrated that the agglutinin titer uniformly rises very early in the course of infection and is almost invariably positive when the patient becomes ill. During recovery the serological titer may return to below 1:100, remain elevated for many months and years, or pursue an undulating pattern corresponding to recurrence of acute symptoms and bacteremia. Recurring acute disease was commoner in infection due to B. melitensis than in that due to B. suis. In instances where the brucellosis skin test was negative before, it had become positive at the onset of symptoms.

The 60 patients were treated in various ways, including therapy with tetracycline and/or streptomycin. There was no apparent effect of treatment upon duration of fever in the acute disease, bacteriological and clinical recurrence, or development of "chronic brucellosis." Similarly, there was no effect of treatment upon the course of fever. The only apparent result of therapy with streptomycin and tetracycline was a more rapid disappearance of bacteremia while the drugs were given.

A number of interesting aspects of brucellosis observed in the group of 60 patients are described, including (1) coexistent pneumococcal pneumonia; (2) symmetrical ulcers of the ankles, due to B. suis; (3) development at different times of tularemia and brucellosis in the same patients, and (4) a Herxheimer reaction associated with recurrent bacteremia seemingly related to treatment with streptomycin and tetracycline.

The occurrence of "chronic brucellosis" is discussed briefly. There was no relationship between development of chronic symptoms following acute brucellosis and serological titer or type of treatment prescribed.

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Brucellosis

II. Medical Aspects of Delayed Convalescence

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Four clinical types of brucellosis were described by Hughes in his classical monograph on "Mediterranean, Malta, or Undulant Fever."[1] These were characterized as malignant, undulatory, mild or intermittent, and irregular or mixed, depending largely upon the severity, duration, and course of the infection. Although brucellosis, as studied by Hughes, was probably due almost exclusively to Brucella melitensis, his classification and description of the disease became widely accepted regardless of the species of Brucella causing infection. Cases were included in Hughes' studies only if the evidence was sufficient to "prove" the diagnosis. Hughes' classification of brucellosis has been criticized in that he did not describe cases of chronic disability.[2] Bassett-Smith, in 1903,[3] however, described patients with "chronic brucellosis" who had persistent ill health, with fatigability and inability to carry on normal activities even in the face of a declining or negative agglutinin titer and without physical abnormalities. Acute brucellosis, diagnosed by rising serological titer or isolation of the bacteria, can occur in the absence of fever or physical abnormalities.[4] The absence of physical abnormalities in "chronic brucellosis," therefore, does not exclude the possibility that the infection may be associated with prolonged ill health. In 1947, Evans[5] began to focus attention upon this form of "chronic brucellosis" as responsible for many instances of long-continued illness and indicated that many of these patients were misdiagnosed as "neurasthenic." The lack of objective evidence, such as fever, suppurative or granulomatous complications, rising serological titer, and positive bacterial cultures, however, makes "chronic brucellosis" a diagnosis difficult to establish.

Sprink[6] provided a follow-up study of 65 patients with serologically and bacteriologically proven acute brucellosis who received no specific therapy and showed that over one-half recovered from the acute illness within one year. Of 30 patients who had symptoms persisting for longer than one year, 5 had relapsing acute disease, 12 had localized lesions of infection, and 13 had no objective evidence of disease. Among 61 patients treated with specific chemotherapy the development of chronic illness was as common, with approximately the same distribution of discernible causes. Depression, sexual impotence, tiredness, and vague aches and pains are the principle symptoms of "chronic brucellosis,"[4] but, whether or not these symptoms are attributable to neuroticism, organic brain damage resulting from brucellosis, functional complaints precipitated by the infection, or lingering undetected infection has not been clearly defined.[6]

Prolonged illness developing after bacteriologically and serologically proven acute brucellosis can be easily attributed to the infection, but establishment of a causal relationship between the two *demands* substantiating evidence. In order to evaluate the relationship between brucellosis and

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chronic illness without physical abnormalities ("chronic brucellosis"), a study of the available patients presented previously [4] was undertaken. Included in the investigation were patients who had completely recovered within one year after their acute infection and patients who continued to complain of poor health.

An attempt has been made to answer certain questions regarding "chronic brucellosis." 1. Are there clinical characteristics of acute brucellosis which might identify those patients most likely to develop chronic symptoms? 2. Are there clinical findings, other than symptoms, which can differentiate the patient who has completely recovered from acute brucellosis and the patient who has "chronic brucellosis?" 3. Are there discernible psychologic factors which could be associated with the occurrence of chronic symptoms in the patient who has had acute brucellosis? The first two questions were specifically investigated and are reported here. The third question was investigated and is reported in Part III of this series.

Acute Brucellosis

Twenty-seven of sixty patients [4] who had had acute brucellosis four to eight years previously were available for follow-up study. Three of these patients were found to have emphysema, bronchiectasis, and nephrolithiasis, respectively, and were excluded from the final evaluation.

The 24 patients studied had contracted their infection in bacteriological laboratories dealing with Brucella suis and B. melitensis. The acute illness was associated with fever, myalgia, backache, headache, tiredness, and malaise in 23 patients. One patient was afebrile. Their Brucella infection corresponded in every respect to that described previously.[4] Five patients had hepatomegaly, and four had splenomegaly (Table 1).

The diagnosis of acute brucellosis was established in 17 patients by isolation of the micro-organism from blood and bone marrow. In the remaining seven patients, the diagnosis was established by a rise of the agglutinin titer to above 1:100. Prior to developing brucellosis, every patient had been examined clinically and by serological test and cutaneous reaction to brucellin or Brucellergin (a suspension of nucleoprotein from Brucella cells). This base line information facilitated accurate appraisal of changing agglutinin titers and appearance of positive skin tests. It was possible, therefore, to make the diagnosis of acute brucellosis with confidence. After the acute infection the patients were followed closely, and repeated serological studies were performed about every six months during the ensuing four to eight years. Sixteen of the twenty-four patients had been diagnosed as having chronic brucellosis on the basis of symptoms of illness that had persisted for about one year or longer after the occurrence of acute brucellosis. Ten of the sixteen patients with chronic brucellosis were still symptomatic at the time of this study, and they will be referred to as the *chronic-symptomatic* group. The other six patients, once diagnosed as having chronic brucellosis, were asymptomatic at the time of the study, and they will be referred to as the *chronic-recovered* group. The remaining eight patients had been well since recovery from their acute brucellosis, and they will be referred to as the *acute-recovered* group.

The patients, as a whole, had about the same mean age—35 years—and there was no difference between the groups regarding year of onset of their acute brucellosis. The number of infections caused by B. suis and B. melitensis was approximately the same in each group.

Patient 7, who was afebrile during his acute infection, did not develop symptoms of chronic brucellosis. The remaining 23 patients had a maximum fever, with temperature ranging from 99 F to 106 F, during the acute disease. Maximum temperature elevations were no higher in the patients who developed chronic symptoms than in those who did not (Table 2). The duration of illness during the acute infection

TABLE 1.—*Laboratory-Acquired Brucellosis in Twenty-Four Patients 4- to 8-Yr. Follow-Up*

	Acute Brucellosis																				4- to 8-Yr. Follow-Up		
						Manifestations									Treatment *				Manifestations												
	Case No.	Age	Sex	Race	Bacteremia ‡	Fever, Headache	Myalgia, Backache	Arthralgia, Fatigue	Malaise, Abd. Pain	Abd. Tend. Hepatomegaly	Splenomeg., Lymphadenopathy	Rhinitis, Pharyngitis	Duration, Days	Max. Agg. Tit.	None	Chloramphenicol	Tetracycline	Streptomycin	None	Fatigue	Headache	Insomnia	Depression	Irritability	Myalgia	Sex. Impotence	Nervousness	Backache	Agg. Titer	Duration Disability, Mo.	Skin React. †
Acute—recovered	1	26	M	W	s	+	+	0	0	0	0	+	7	1,600	0	0	+	+	+									50	2.0	1,000
						+	0	+	0	0	0	0																		
	2	30	M	O	0	+	0	0	+	0	0	0	5	6,400	+			+										50	0.25	10,000
						+	0	+	0	0	0	+																		
	3	31	M	W	s	+	0	+	+	0	0	0	21	3,200	0	0	+	+	+									50	1.25	1,000
						+	0	0	+	0	0	0																		
	4	36	M	W	s	+	+	+	0	0	0	0	12	3,200	0	0	+	+	+									200	6.0	ND
						0	0	0	0	0	0	0																		
	5	46	M	W	m	+	+	0	0	0	0	0	15	3,200	0	0	+	+	+									25	1.25	ND
						+	+	0	0	+	+	0																		
	6	28	M	W	s	+	+	0	+	0	+	0	8	3,200	0	0	+	+	+									50	2.0	1,000
						+	0	+	0	+	+	0																		
	7	29	M	W	0	0	0	0	0	0	0	0	10	200	0	0	+	+	+									50	2.0	1,000
						+	+	0	+	0	0	0																		
	8	38	M	W	s	+	0	+	0	0	0	0	21	12,800	0	0	+	+	+									100	2.0	10,000
						+	+	0	0	+	0	0																		

Chronic—recovered	9	32	M	W	0	+	0	+	0	0	0	0	12	400	0	0	+	+	0	+	0	0	0	0	0	0	0	0	0	10.0	1,000
						0	0	0	0	0	+	0																			
	10	32	M	W	s	+	0	0	+	0	+	0	15	800	0	0	+	+	0	+	+	+	0	0	0	0	0	0	25	18.0	100
						+	+	+	0	0	0	0																			
	11	35	M	W	0	+	+	0	+	0	0	0	10	6,400	0	0	+	+	0	+	0	0	+	+	0	0	0	0	100	60.0	100
						+	0	+	0	0	0	0																			
	12	39	M	W	s	+	0	+	+	+	0	0	16	1,600	0	0	0	+	0	+	0	0	0	0	0	0	0	0	200	36.0	10,000
						+	0	+	0	+	0	+																			
	13	34	M	W	s	+	+	0	+	0	0	0	21	6,400	0	0	+	+	0	+	+	0	0	0	+	0	0	0	50	18.0	ND
						+	+	0	0	0	0	0																			
	14	37	M	W	s	+	0	+	+	0	0	0	120	3,200	Sulfonamide				0	+	0	0	+	0	0	0	0	0	50	36.0	1,000
						+	0	0	0	+	0	0																			
Chronic—symptomatic	15	31	M	N	s	+	+	0	+	0	+	+	20	800	0	0	+	+	0	+	0	0	0	0	+	0	+	0	50	40.0	1,000
						+	+	0	0	0	0	+																			
	16	38	M	W	0	+	0	0	+	0	0	0	14	400	0	0	+	+	0	+	0	0	0	0	+	0	0	0	50	72.0	1,000
						+	0	+	0	0	0	0																			
	17	31	M	W	s	+	+	0	+	0	0	0	6	1,600	0	0	+	+	0	+	0	0	+	0	+	0	0	0	100	60.0	100
						+	+	0	0	+	0	0																			
	18	30	M	W	s	+	0	+	0	0	0	+	6	3,200	0	0	+	+	0	0	+	0	+	0	0	0	0	0	50–200	36.0	ND
						+	0	+	0	0	0	+																			
	19	32	F	W	m	+	+	0	0	0	0	0	10	12,800	0	0	+	+	0	+	0	0	+	0	0	0	+	+	25	72.0	ND
						+	+	+	0	0	0	0																			
	20	32	M	W	0	+	+	0	+	0	0	0	7	1,600	0	0	0	+	0	+	+	0	0	0	+	0	0	+	0	96	1,000
						+	0	0	0	0	0	+																			
	21	51	M	N	m	+	+	0	0	0	0	0	20	3,200	0	0	+	+	0	+	0	0	+	0	+	+	0	0	100	72.0	1,000
						+	+	0	+	0	0	0																			
	22	39	M	W	0	+	+	+	0	0	0	0	Indef.	3,200	0	0	+	+	0	+	+	0	+	0	0	+	0	0	400	24.0	1,000
						+	+	+	0	0	+	0																			
	23	43	M	W	s	+	+	0	0	0	0	0	Indef.	12,800	0	+	0	+	0	+	+	0	0	0	0	0	0	0	50	30.0	100
						+	0	0	0	0	+	+																			
	24 §	36	M	W	s	+	+	0	+	0	+	0	15	800	0	0	+	+	0	+	+	0	+	0	+	0	+	0	50	36.0	ND
						0	0	0	0	+	0	+																			

* Streptomycin=1 to 2 gm. per day for 10 to 14 days; tetracycline=2 to 4 gm. per day for 10 to 14 days; chloramphenicol=2 to 3 gm. per day for 10 to 14 days.
† Dilution Brucellergin (1:1,000,000; 1:10,000; 1:1,000; 1:100) giving a positive reaction; ND=not done.
‡ s=B. suis; m=B. melitensis.
§ Patient developed sternomanubrial synovitis 3 years after acute brucellosis and eight months after acute tularemia.

TABLE 2.—*Maximum Fever with the Acute Infection*

Temperature, F	Patients, No.		
	Acute-Recovered	Chronic-Recovered	Chronic-Symptomatic
Afebrile	1	0	0
99-100	0	1	2
101.1-101	0	0	0
101.1-102	1	2	1
102.1-103	1	1	2
103.1-104	3	1	2
104.1-105	2	1	3
Total	8	6	10

of each person was calculated, particular attention being paid to the duration of fever, including febrile recurrences. As a rule fever persisted for 1 to 25 days, and there was no significant difference between the acute-recovered and the chronic groups of patients (Table 3).

TABLE 3.—*Duration of Fever with the Acute Infection*

Days	Patients, No.		
	Acute-Recovered	Chronic-Recovered	Chronic-Symptomatic
Afebrile	1	0	0
1-2	1	0	2
3-5	2	2	4
6-8	2	1	2
9-15	1	1	1
16-25	1	2	1
Mean, Days	6.5	10.5	4.9

Comparison of the serological patterns for each group of patients showed that most of them had titers less than 1:100 after subsidence of the acute brucellosis whether they developed chronic illness or not (Table 4), and this did not vary appreciably after the first year of follow-up. In addition, the highest agglutinin titers observed in the patients during the acute infection did not differ when the groups were compared (Table 1).

TABLE 4.—*Serological Pattern Following Initial Illness*

Serological Titers	Patients, No.		
	Acute-Recovered	Chronic-Recovered	Chronic-Symptomatic
Less than 1:100	6	4	6
Higher than 1:100	2	2	4

Hepatomegaly, splenomegaly, other physical abnormalities, and laboratory findings (including tests of liver function) associated with acute brucellosis occurred no more commonly in persons who developed "chronic brucellosis" than in those who did not. Chronic symptoms of ill health were the only complications of the acute infection in the 24 patients studied.

Twenty-two of the twenty-four patients received streptomycin (1 to 2 gm. per day for 10 to 14 days) and tetracycline (2 to 4 gm. per day for 14 to 21 days) as treatment during their acute infection. There was no effect of this therapy in preventing the occurrence of "chronic brucellosis" (Table 5).

TABLE 5.—*Specific Treatment During the Acute Infection*

Treatment	Patients, No.		
	Acute-Recovered	Chronic-Recovered	Chronic-Symptomatic
None	1	0	0
Sulfonamide	0	1	0
Streptomycin *	0	1	1
Streptomycin + tetracycline †	7	4	9
Total	8	6	10

* Streptomycin, 1 or 2 gm. per day for 10 to 14 days.

† Streptomycin + tetracycline; streptomycin, as above, + tetracycline, 2 to 4 gm. per day for 14 to 21 days.

All of the patients with chronic disability (chronic-symptomatic and chronic-recovered) were given one or more additional courses of tetracycline in an attempt to treat their illness but without benefit. Cortisone or hydrocortisone was also administered to a few of the patients with "chronic brucellosis" and was occasionally associated with improvement in the sense of well-being while the drug was given, but there was no evidence of lasting improvement. After subsidence of the acute infection, fever and

other physical abnormalities which could be attributed to active Brucella infection or specifically associated with the chronic illness were not detected.

The clinical and laboratory data observed during acute brucellosis in the 60 patients from which this group of 24 subjects was obtained were described in detail previously.[4] Evaluation of the patients specifically involved in this study failed to indicate any difference between the features of the acute infection in patients who recovered completely from their disease and those in patients who had a lingering chronic illness.

Clinical Findings in Chronic Brucellosis

At the time of this study, four to eight years after the patients had had acute brucellosis, each was hospitalized for detailed clinical study. There were no physical abnormalities of importance. Two of the ten subjects in the chronic-symptomatic group had a past history of tularemia; otherwise there were no historical data which might have a bearing upon the development of "chronic brucellosis." Laboratory findings in the patients (including hemogram, urinalysis, serum proteins, cholesterol, alkaline phosphatase, cephalin flocculation, thymol turbidity, sulfobromophthalein [Bromsulphalein] excretion, nonprotein nitrogen, and electroencephalogram) were for the most part normal, although two patients in the acute-recovered group had serum bilirubin elevations of 3.0 and 2.2 mg. %, respectively, without evidence of impaired liver function or anemia. Nine of the twenty-four patients had an electroencephalogram which was judged to be abnormal.* Two of these nine patients, however, had a distant past history of head injury. The remaining seven abnormal electroencephalograms were distributed evenly between the patients with "chronic brucellosis" and the acute-recovered group. Neurological examination of the patients was normal.

The patients with chronic symptoms described their illness as fluctuating in severity, but few patients were ever symptom-free. In order of frequency, the principle symptoms of the patients with chronic brucellosis were fatigue, headache, nervousness, depression, legache or backache, generalized aching, and sexual impotence.

Two of the patients were still working with Brucella in the laboratory at the time of the study. One of these patients was in the acute-recovered group, and the other was in the chronic-symptomatic group. The remaining 20 patients, on whom information was available, had not worked with Brucella for periods ranging from one to eight years (Table 6). There were no differences between the groups, concerning whether or not they had continued to have intimate contact with Brucella, which could explain the persistence of ill health in those patients with "chronic brucellosis."

TABLE 6.—*Period of Time Since Last Laboratory Contact with Brucella (Twenty-Two Patients)*

Years	Patients, No.		
	Acute-Recovered	Chronic-Recovered	Chronic-Symptomatic
0	1	0	1
1	1	1	1
2	1	0	0
3	2	1	5
4	2	0	0
5	0	1	0
7	0	1	0
8	0	1	1
Mean, Yr.	2.8	4.8	3.4

An evaluation of the degree of hypersensitivity of the patients to Brucellergin was accomplished by skin-testing 18 of the subjects with dilutions of the antigen ranging from 1:100,000 to 1:100. The material (0.1 ml.) was injected intradermally into the forearm, and the reaction was read at 24 and 48 hours. If no reaction was observed, the next strongest dilution was injected in the opposite forearm. A positive

* Electroencephalograms were interpreted independently by Dr. Curtis Marshall, Phipps Institute, The Johns Hopkins Hospital.

reaction was characterized by edema, erythema, and induration of about 10 mm. in diameter persisting for 48 hours. There were no differences in the degree of hypersensitivity to Brucellergin between the patients diagnosed as having "chronic brucellosis" and those who had recovered completely from the acute infection (Table 1). None of the patients had a negative skin reaction to the antigen dilutions used in the tests.

Intensive clinical and laboratory study of the patients, therefore, did not reveal any significant differences between those with acute-recovered or "chronic brucellosis" and failed to indicate anything which could serve to identify the person with "chronic brucellosis," other than his persistent symptoms of poor health.

Comment

None of the chronically ill patients presented in this follow-up study of proven brucellosis had a relapsing febrile illness, nor did they have localized infection due to Brucella which could explain their long-continued poor health. They, therefore, fall into a third category of "chronic brucellosis," clearly delineated by Spink [6] and characterized by illness in the absence of objective evidence of disease. Their symptoms were uniformly those of fatigue, headache, nervousness, depression, legache and backache, generalized aching, and sexual impotence. Compared with a group of patients who developed acute brucellosis at about the same time, i. e., four to eight years previously, but who recovered promptly, there were no discernible differences in severity, duration, or physical or laboratory findings detected with the acute infection. Similarly, there were no differences regarding species of organism causing the infection or type of therapy given during the acute disease. Serological responses, likewise, were the same in patients who recovered completely from acute brucellosis and those who developed a chronic illness. Findings from physical examination and laboratory studies of patients who had "chronic brucellosis" did not differ from those of patients who had recovered from brucellosis.

All of the persons studied were shown to be hypersensitive to the antigens of Brucella, but there was no detectable difference in the degree of hypersensitivity to Brucellergin between the groups of patients. Some of the subjects, chronic as well as recovered, had continued to have contact with Brucella for a period of time after their acute infection. All but two of the patients, however, had ultimately been removed from contact with the micro-organism but without improvement in those with "chronic brucellosis." Although allergic reactions occasionally have been considered to be responsible for recurrence or persistence of symptoms in "chronic brucellosis," this certainly would not seem to have been a factor here.

Spink [6] listed three possible explanations for the complaints associated with chronic disability following brucellosis. These were (1) continued active Brucella infection, (2) possibly psychoneurotic or neurasthenic patients, and (3) possible organic brain damage as a result of the acute brucellosis, producing the nonspecific symptoms of ill health.

In this study it has been demonstrated that there was no evidence of persistent infection with Brucella in the patients. Prolonged elevation of agglutinin titer above 1:100 in some persons and persistence of hypersensitivity to Brucellergin might be indicative of continued presence of Brucella in the tissues. These findings, however, were no different in patients who recovered completely from those in patients who remained in ill health after the acute infection.

Although several persons had minor abnormalities on electroencephalogram, this was as frequently found in the recovered as in the chronically ill patients. Organic brain damage detected by this means, therefore, was not a feature of "chronic brucellosis."

The incidence of "chronic brucellosis" among the 60 patients from whom this follow-up study was possible (40%)[4] seems to be considerably higher than the incidence of "chronic brucellosis" in other series.[6] An explanation for this is not readily apparent. It is possible that the close surveillance of the personnel, arising from the nature of their occupation in laboratories dealing with infectious agents, enabled and perhaps encouraged the recognition of symptoms which otherwise would not have come to the physician's attention. In addition, "chronic brucellosis" is a widely recognized, though variably diagnosed, entity, and in these proven cases of acute brucellosis it is probable that vague symptoms of ill health following the acute infection were commonly interpreted as such. It was not possible to associate the diagnosis of "chronic brucellosis" with any particular physician, but among the employees "chronic brucellosis" is an accepted occasional consequence of acute brucellosis, facilitating their relating chronic symptoms to the acute Brucella infection.

The information obtained from this study does not suggest an association between "chronic brucellosis" and persistent infection or residual organic damage in the afflicted patient. The resemblance of the symptoms of "chronic brucellosis" to psychoneurosis suggests the possibility that psychologic factors may be of importance in the pathogenesis of the illness. Evaluation of these relationships is presented in the following paper.

Summary

Twenty-four patients were studied who had had acute brucellosis due to infection with Brucella suis or Brucella melitensis four to eight years previously. Sixteen of these persons had developed symptoms of depression, fatigue, sexual impotence, and vague aches and pains after the acute disease and were diagnosed as having "chronic brucellosis." The other eight patients had recovered completely from their acute infection. Clinical study of the subjects did not demonstrate a difference between the two groups except for the continued symptoms of poor health. Serological and other laboratory tests were no different between the two groups of patients. Electroencephalograms showed no evidence of organic brain damage which could be incriminated as responsible for the "chronic brucellosis."

It was impossible to delineate those patients with acute brucellosis who were likely to develop chronic disability. Furthermore, the patients with "chronic brucellosis" had no clinical characteristics which would differentiate them from subjects who recovered uneventfully from acute brucellosis, except for their complaints of ill health. The resemblance of "chronic brucellosis" to neurosis, therefore, suggested that psychologic factors might be of importance in the pathogenesis of this disorder.

The Johns Hopkins Hospital (5).

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Brucellosis

III. Psychologic Aspects of Delayed Convalescence

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Brucellosis is usually a self-limited disease. Complications, such as suppurative or granulomatous lesions, may, however, occur. In addition, some patients remain disabled after the acute infection because of persistent symptoms in the absence of any demonstrable physical abnormalities and are commonly said to have "chronic brucellosis." The present study was done to investigate the role of psychologic factors in the pathogenesis of this delayed convalescence.

"Chronic brucellosis" is clinically similar to neurosis in that nonspecific symptoms, such as fatigue, headache, myalgia, arthralgia, "nervousness," and depression, occur in the absence of abnormal physical findings. This similarity could be attributed to factors discussed below, which may be important determinants in delayed convalescence from any illness.

1. Although similar to emotional illness, "chronic brucellosis" might be unrelated to psychologic factors and be attributed to enduring infection. The coexistence of neurosis and "chronic brucellosis" then would be no more than expected from chance alone.

2. It is possible that "chronic brucellosis" reduces the patient's capacity to adapt to his environment. If this were the case, the patient would be faced with the frustrating circumstance of being neither sick enough to be restricted to bed nor well enough to carry on everyday activities comfortably. He might react to this situation (over a significant period of time) with loss of self-esteem or with chronic anxiety with its manifold derivatives. In connection with this postulated reduction of adaptive capacity, Apter et al.[1] suggested that "chronic brucellosis" is associated with organic brain damage resulting from the acute infection.

3. Another explanation for the apparent similarity of neurosis with "chronic brucellosis" might be a decrease in resistance to infection in the person with concurrent emotional stress. The emotionally disturbed person therefore may be particularly susceptible to persistent infection.

4. Finally, some patients may be suffering from psychoneurosis that is mislabeled "chronic brucellosis."

In the preceding paper[2] it was shown that patients with "chronic brucellosis" could not be distinguished by clinical and laboratory examinations from those who had recovered uneventfully after acute brucellosis. The two groups (chronic and acute-recovered) were identical with regard to severity, course and treatment of the acute disease, strain of Brucella causing the infection, and pattern of serological response. No evidence of persistent infection or residual physical disability in the patients with "chronic brucellosis" was found. The purpose of the present study was to determine if the patients with "chronic brucellosis" could be distinguished from the acute-recovered group by psychological and psychiatric examinations.

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TABLE 1.—*Data on Twenty-Four Patients with a Past History of Acute Brucellosis*

	Patients, No.	Duration of Illness *	Time Since Onset of Illness *	Age, Yr.*	Occupation	
					Professional	Nonprofessional
Acute—recovered	8	2.1 mo.	4.4 yr.	35.1	6	2
Chronic—recovered	6	1.7 yr.	6.2 yr.	35.5	5	1
Chronic—symptomatic	10	4.5 yr.	4.5 yr.	35.6	4	6

* These entries are the mean values.

Material and Methods

Description of Clinical Material.—Twenty-four patients with a history of acute brucellosis two to eight years previously were hospitalized for three days for psychologic study.

The medical investigation of these patients was reported in the preceding paper.[2] The initial infections were with Brucella suis or Brucella melitensis and had been acquired from occupational exposure in a bacteriology laboratory. On the basis of their present symptomatic status and history the patients were divided into three groups:

(1) Acute-Recovered: Eight persons who became asymptomatic within about eight months after the initial infection and who have subsequently considered themselves well.

(2) Chronic-Recovered: Six persons who remained symptomatic for one year or longer after their initial infection but who had become asymptomatic prior to this study.

(3) Chronic-Symptomatic: Ten persons who were still having symptoms at the time of this investigation, two years or more after their acute infection.

Duration of illness, time elapsed between the onset of illness and the present study, and ages of the patients are summarized in Table 1. The ages, sex distribution, marital status, and race of the three groups were similar. The one female patient was in the chronic-symptomatic group. The subjects were Caucasian except for two Negroes in the chronic-symptomatic group and one Oriental in the acute-recovered group. There were two unmarried persons in the acute-recovered group and one in each of the two chronic groups.

The patients could be separated according to socioeconomic level and occupation. Fifteen were bacteriologists or biochemists engaged in research or administration. Nine persons, with high school education or less, were employed in semiskilled or unskilled work, and one of these was illiterate. As shown in Table 1, all but 3 of the acute-recovered and chronic-recovered patients were "professional" employees, while 6 of the 10 chronic-symptomatic patients were "nonprofessional" employees.

Method of Psychologic Study.—To investigate the possibility of deficit associated with organic brain damage, certain specific areas of intellectual functioning were evaluated by the following psychological tests.

(1) Vocabulary Test from the "Wechsler Adult Intelligence Scale": This serves as a valid short index of intelligence level, correlating as highly with the total I. Q. as many I. Q. tests correlate among themselves.[3]

(2) Retention of Logical Material: Memory for content of two paragraphs presented orally to the subject by the examiner.[4]

(3) Test for visual memory.[4]

(4) Test for associate-learning.[4]

(5) Digit-symbol substitution test.[5]

The latter four tests were chosen to determine the ability of the subject to maintain attention, recall, learn new associations, and sustain motor speed, all in an efficient manner. To obtain an indication of possible deficit in intellectual functioning, the scores of each person on these tests were evaluated with respect to his intellectual-ability level as previously determined by the vocabulary test.

Each patient was also given the Bender-Visual-Motor-Gestalt Test[6] to study visual motor coordination and signs of possible perceptual confusion. This test, unlike those mentioned above, has no objective scoring system, and its interpretation could be influenced by the bias of the examiner. An attempt was made to overcome this possibility by pooling the judgments of the examiner with those of two other psychologists who were familiar with the test but not with the purpose of the study.

To assess personality functioning, each patient was administered the Minnesota Multiphasic Personality Inventory (MMPI),[6] which requires the subject to respond to a large number of questions pertaining to feelings, attitudes, reaction tendencies, and experiences as being either true or false of himself. The MMPI was originally standardized on an empirical basis, i. e., in persons who had been psychiatrically studied and diagnosed and in subjects who were considered normal. On this basis it was found that the items of the MMPI could be separated into groups, or "diagnostic keys," corresponding to various clinical categories. There were thus developed the hypo-

chondriasis (Hs), depression (D), psychasthenia (Pt), and hysteria (Hy) keys used in this study. For purposes of the present study, a "Neurotic Index" was defined as the average of the Hs, D, and Hy scores for each person. Also used was a key tentatively called the morale-loss index, which was developed by one of us (A. C.) in a study in which the MMPI had been administered to a group of subjects, all of whom had attempted suicide. Finally, an additional personality test called the Self-Concept Scale[7] was administered. This scale consists of about 100 items and provides indices of the degree to which a subject perceives himself positively or negatively in regarding his own worth in terms of moral-ethical values, emotional or psychologic adaptability, and interpersonal relations and his worth in terms of physical self.

Although the scores from the above personality tests are derived in an objective manner and are not influenced by bias, the psychologist was not informed of the clinical classification of each patient until the tests were completed.

The patients were psychiatrically interviewed daily during a three-day period of hospitalization. The interviews were recorded and transcribed. The interviewer attempted to gain an over-all impression of the present emotional or psychologic condition of each subject. It was difficult to exclude the possibility of unconscious bias of the observer, but, in an effort to minimize this, the interview material was analyzed in terms of factual historical data, which in themselves would be clearly independent of or antecedent to the patient's brucellosis and which also would be indicative of emotional stress. The patients of both chronic groups were considered together and compared with the acute-recovered group in terms of gross evidence of environmental conditions or events associated with psychologic trauma or deprivation in childhood. The chronic and acute-recovered groups were also compared in terms of disturbed or "troubled" life situations which existed at the time of the acute infection or which had begun and persisted during the year before or after the acute phase of the illness.

Results

Psychological Tests.—The chronic-recovered and acute-recovered groups had a significantly higher intelligence level than the chronic-symptomatic group; this finding seems to be consistent with the greater proportion of professional employees in the two recovered groups. When the scores of the tests of recall, learning, and psychomotor speed were evaluated with respect to the intellectual-ability level, no significant differences were found that distinguished the two chronic groups from each other or from the acute-recovered group or from the general population. Thus there was no evidence of significant impairment of intellectual function.

The Bender-Visual-Motor-Gestalt also failed to reveal significant differences between the performances of subjects in the three groups. The Bender test results of two patients were judged to be equivocally indicative of organic brain damage; one of these patients was in the chronic group, and the other, in the acute-recovered group.

In contrast to the tests evaluating intellectual functioning, the personality tests showed definite trends and differences among the groups.* As might be expected, the hypochondriasis score, which reflects preoccupation with somatic symptoms, was significantly higher in the chronic-symptomatic group than in either the chronic-recovered or acute-recovered groups, both of which were more within the normal range for this score. However, the depression and psychasthenia scores, morale-loss index, and "average neurotic" index were significantly higher in both of the chronic groups than in the acute-recovered group. The Self-Concept Scale supported these findings in that both of the chronic groups had significantly fewer positive self-concepts than the acute-recovered group.

The two chronic groups are distinguished from each other by their self-concept scores in that the chronic-symptomatic group tend to regard themselves as relatively "normal" with respect to emotional health but poor with respect to physical health. The chronic-recovered patients, on the other hand, tended to have comparatively negative attitudes about their emotional health and approximately normal physical-self attitudes.†

* The significance of the differences among the means of the various personality test scores was determined by analysis of variance.

† The differences on the Self-Concept Scale between the two chronic groups were significant as determined by the *t*-test.

TABLE 2.—*Comparison of Test Results and Personal Histories of Twenty-Four Patients*

	Patient	WAIS*	MMPI Scores †							Gross Evidence of Environmental Stress	
		Vocab.	Hs	D	Hy	AvN	Pt	Mt	S-C	Childhood	Concurrent Life Situation
Acute-recovered	1	14	52	44	58	51.3	50	1	96	None	None
	2	16	62	68	62	64.0	62	6	51	None	None
	3	13	52	46	56	51.3	52	2	106	Parents divorced	None
	4	16	44	56	53	51.0	42	1	120	None	None
	5	15	57	44	58	53.0	52	4	129	None	None
	6	13	49	58	60	55.7	46	0	141	Very frequent moves	None
	7	15	54	44	60	52.7	46	4	146	None	None
	8	8	52	48	56	52.0	50	3	107	None	None
Chronic-recovered	9	15	44	70	53	55.7	62	12	19	Alcoholism, father; chronic compl. mother; disrupted home	None
	10	10	70	63	47	60.0	66	12	61	Harshly punitive mother	Death of relative; anxiety re courtship & marriage
	11	15	54	60	56	.7	56	5	79	None	Conflictful situation involving fiancee & mother
	12	16	52	75	67	62.7	77	10	40	Dominating, overprotective mother	None
	13	14	52	48	64	54.7	50	1	131	Death of father, home disrupted	None
	14	13	57	68	62	62.3	66	9	56	None	Death of mother; academic failure
Chronic-Symptomatic	15	7	59	80	75	71.3	54	8	‡	None	Difficulties at work; illness & death of father; illness of mother
	16	12	49	53	49	50.3	62	11	93	None	Death of mother; wife had 2 miscarriages; illness of father
	17	11	65	56	60	63.7	50	5	100	Mother emotionally ill, father seldom home	Serious difficulties at work
	18	13	47	63	51	53.7	81	12	94	Alcoholism father, chronically compl. mother	Illness of mother & father; conflictful feelings about work
	19	14	76	69	75	73.3	81	10	63	Father chronically irritable; 1 sibl. chronically ill; felt rejected	Conflictful situation regarding courtship
	20	9	57	58	55	56.7	52	1	94	Alcoholism father; asthmatic brother who was later psychotic	Illness of father; apparent sterility of marriage; disability pension discontinued
	21 §	7	—	—	—	—	—	—	—	None	Serious marital conflicts; illness & death of father; illness of mother
	22	10	93	68	82	81.0	58	6	111	Death of father; temporary disruption of home	None
	23	12	70	58	64	64.0	58	8	91	Depressed rigid father	Severe conflict with family; dislikes present work; illness of mother
	24	9	67	68	65	66.7	48	6	113	Death of brother	None

* Wechsler Adult Intelligence Scale.
† Minnesota Multiphasic Personality Inventory.
‡ No data; test not taken.
§ Patient illiterate; remaining tests not given.

The personality-test scores for each person are given in Table 2, and the mean values for the three groups, in Table 3.

Psychiatric Interviews.—Most of the patients indicated that they had agreed to cooperate with the study because it afforded them an opportunity to get a thorough physical "check-up" by competent physicians at no personal expense; this was, of course, particularly important to the 10 chronic-symptomatic patients. Many subjects, especially those who were engaged in research, stated that they were willing to participate because this was a research project. None

TABLE 3.—*Mean Scores of the Patients on the Personality Tests*

	Hs*	D*	Pt*	AvN*	Ml*	S-C
Normal	48.2	49.4	48.2	50.5		
Acute-recovered	52.8	51.0	50.0	53.9	2.7	112
Chronic-recovered	54.8	64.0	62.8	58.7	8.2	64.3
Chronic-symptomatic	64.8	63.7	60.4	64.5	7.4	94.9

* MMPI scales described in "Method of Psychologic Study."

of them explicitly voiced resentment about the matter of taking psychological tests and being interviewed by a psychiatrist. Regarding their implicit attitudes, however, there were distinct differences among the three groups.

The chronic-symptomatic patients tended to be considerably more resistant to the discussion of personal issues than were the two recovered groups. In this connection, it is of interest that the clinical history of one subject who declined to participate in the study revealed that he would be in the chronic-symptomatic group. These patients expressed the belief that they were afflicted with an organic disease called "chronic brucellosis." They also conceived of "chronic brucellosis" as being capable of producing practically any sort of subjective discomfort, and they tended to use their diagnosis as a readily available explanation for any disturbance in their sense of well-being.

The chronic-recovered patients, who considered themselves physically well and were not preoccupied with bodily symptoms, were as a whole far less defensive and resistant to discussing personal issues, and they tended to be more aware of having emotional problems.

It was the interviewer's impression that the 16 patients in the two chronic groups showed considerably more evidence of emotional disturbance than did the acute-recovered group. The majority of the "chronic" patients appeared depressed to a moderate degree, often with symptoms of overt anxiety. In addition, three of them appeared to be borderline schizophrenic and in several hysterical features were present.

The eight acute-recovered patients were also less defensive than the chronic-symptomatic group. Seven of the eight were asymptomatic, relatively free to discuss their personal lives, and were generally rather energetic or enterprising people. The major exception to this general description is a person who did seem depressed, had some somatic symptoms, and was very reticent but who did not regard himself as having "chronic brucellosis" (Patient 2).

It is of interest that most of the patients in the three groups viewed brucellosis as an acute infection that is often followed by a protracted period of illness, i. e., that the development of chronic symptoms is very common. The acute-recovered patients regarded themselves as simply fortunate.

Analysis of the biographical data obtained during the psychiatric interviews revealed gross evidence of psychologically traumatic events or circumstances in the childhood environments in 11 of the 16 chronically ill patients and in 2 of the 8 acute-recovered persons; this is a statistically significant difference ($P<0.05$, Fisher's method). These 11 persons reported the following difficulties: Three described their fathers as alcoholics; two of these three also had chronically complaining mothers, and the third had an asthmatic brother who later became psychotic. Two reported paternal death during their childhood. One reported that his brother, two years younger, died during childhood, thus restoring the patient to the position of "baby" in the family. Two patients described extremely punitive or dominating attitudes in one parent, with the other parent being ineffectually in the background. Three described apparent emotional disturbances in the form of chronic depression or "nervous breakdown" in one parent. Among the acute-recovered patients, one reported that parental divorce occurred early in his life and one reported that his family moved from one city to another very frequently, which may have reduced his sense of security and belonging.

Analysis of the data for evidence of disturbed or "troubled" life situations existing at the time of the acute infection or which had begun and persisted during the year before or after the acute phase of the illness revealed significant differences between the chronic and the acute-recovered patients. Eleven of the sixteen chronically ill subjects were experiencing significant stresses of some sort during that particular period of their lives, as opposed to none of the eight recovered patients. These difficulties varied considerably, and often it was apparent that a number of factors were involved in the life of a patient: death or serious illness of a close member of the family (seven patients), overtly conflictful interpersonal situations involving the family (five patients), and serious failure in work (two patients).

Comment

Psychological tests evaluating certain specific areas of *intellectual functioning* did not reveal significant differences between the patients with "chronic brucellosis" and those who had recovered uneventfully from the acute infection. These tests, as well as the neurological examinations and the EEG's as previously reported,[2] did not provide support for the view that the persons with "chronic brucellosis" had suffered organic brain damage sufficient to impair intellectual capacity for adaptation. It was also noted in the preceding paper [2] that evidence for persistent Brucella infection, hypersensitivity, or any other physical abnormality failed to distinguish our patients with "chronic brucellosis" from those who were asymptomatic after the acute infection.

In the present study, however, psychological tests and psychiatric interviews performed independently revealed that *emotional disturbance* was significantly more prevalent in the "chronic" groups than in the acute-recovered group. Depression seemed to be a prominent feature of the emotional disorders that we observed.

In spite of the negative results of careful medical evaluation, the possibility arises that the patients with "chronic brucellosis" were emotionally disturbed as a *consequence* of persisting symptoms of their disease. The following observations, however, suggest that this was not the case:

1. Psychological tests revealed evidence of emotional disturbance in the chronic-recovered as well as in the patients who were still symptomatic at the time of the study.

2. Biographical data obtained from the psychiatric interviews revealed the existence of emotionally stressful events or circumstances in childhood and in the period concurrent with the acute Brucella infection. These events and circumstances were antecedent to or otherwise independent of the Brucella infection and could not be reasonably viewed as merely secondary to the latter.

Taken together, the results presented in this and the preceding paper support the view that "chronic brucellosis" consists essentially of an emotional disorder. The findings suggest that symptomatic recovery from acute brucellosis depends critically on the emotional state of the person at the time of the acute infection or in the convalescent period. In the wake of an acute Brucella infection there is almost always a period of lassitude or fatigability. In the depressed patient these otherwise transient symptoms merge imperceptibly with depressive fatigue or lassitude and thus appear to be perpetuated. The manifestations of the patient's emotional disturbance thus become included, by the patient and often by his physician, in the syndrome of "chronic brucellosis." In addition, it is our impression that neurotic symptoms tend to be intensified and modified by the symptom pattern of the acute illness.

It is likely that the traumatic early life experiences of most of our chronically ill patients rendered them vulnerable to a depressive reaction to interpersonal "loss" or threat of loss in adult life. If the depressive

reaction and the acute Brucella infection more or less coincide, the development of a syndrome labeled "chronic brucellosis" is apt to ensue. If the temporal relationship between the depressive reaction and the acute illness are not close, it is far less likely that the symptoms of the former will be attributed to brucellosis, as illustrated by Patient 2.

It was noted that in three of the six chronic-recovered patients the alleviation of symptoms occurred more or less concurrently with resolution of certain personal difficulties in their lives. Ten of the sixteen chronically ill persons, however, were still symptomatic five years, on the average, after the acute illness. This tenacity of the symptoms was impressive. In the preceding paragraphs we have described a mode of development of this delayed convalescence that seems to be supported by the data. However, once the chronic syndrome is established and is firmly labeled "chronic brucellosis," other factors are added which favor its continuation.

The results of the Self-Concept test offer a clue as to the nature of one of these factors. The chronic-symptomatic patients regarded themselves as more emotionally healthy or adaptable than did the chronic patients who no longer had their somatic symptoms. The latter group tended to see themselves as having emotional difficulty, while the chronic-symptomatic patients thought of themselves as physically ill. This suggests that the somatic symptoms have a self-esteem-supporting function. This possibility is in keeping with the observation that the chronic-symptomatic patients tended to make use of their "chronic brucellosis" as a readily available explanation for any discomfort that occurred. They were, therefore, less inclined to relate their anxieties or feelings of depression to personal issues or problems.

In our patients, there is the possibility that potential financial compensation played a role in the persistence of symptoms. However, we have no direct evidence of this. It is apparent that this factor alone is certainly insufficient, since all the patients, including the recovered persons, would be eligible for disability compensation.

We do speculate that the reputation of brucellosis as a chronic disease supports the patient's tendency to retain his symptoms for long periods of time. The articles of Evans [8] played an important historical role in calling the attention of the public and the profession to chronic brucellosis as a disorder which is often mislabeled "neurasthenia." However, the results of the present study lead us to conclude that emotional disturbance constitutes the essential component of the syndrome.

Summary

Twenty-four patients with a history of acute brucellosis four to eight years previously were given a battery of psychological tests and psychiatric interviews. Sixteen of these persons had developed a chronic subjective syndrome after the acute illness, and ten of them were still symptomatic at the time of this study. Eight patients had recovered uneventfully after the acute infection.

Psychological testing of certain specific areas of intellectual functioning did not reveal evidence of organic brain damage in either the chronic or the acute-recovered groups.

Independent evaluation of our patients by psychological testing and psychiatric interviews did reveal evidence of emotional disturbance, especially depression, in the chronically ill patients. Analysis of the data supports the view that the emotional disturbance is not merely secondary to the stress of illness but is more critically related to the pre-illness personality structure and the concurrent life situation.

Factors which favor the protracted continuation of the chronic syndrome, once it is established, include the maintenance of self-esteem afforded by somatic symptoms, as an alternative to recognition of psycho-

logic difficulty, and the notorious reputation of brucellosis as a chronic disability.

Our findings, in conjunction with those of the preceding paper in this series, support the view that emotional disturbance is the essential component of "chronic brucellosis."

Report of Cases

PATIENT 2.—This patient in the acute-recovered group was of special interest. An unmarried man contracted brucellosis about six years before this study, experienced the usual symptoms of the acute febrile illness, and recovered rather quickly and completely, as far as he was concerned. At that particular time of his life, the patient was satisfied with his job and had a sense of responsibility and interest in his aging parents and younger siblings. His responsible role in the family was more or less assigned to him as part of the cultural tradition of his immigrant parents and was accepted and was perhaps especially important to him, since he was a bachelor. Approximately two years after the episode of acute brucellosis his life situation began to change. His mother became afflicted with a serious chronic illness; his younger siblings went on their own ways more or less independently; his parents returned to their homeland, and he wondered if he would see them again. In this situation, the patient became socially withdrawn, developed vague somatic complaints, including headache and fatigability, and appeared both clinically and by psychological testing somewhat depressed. The patient and physician, however, did not consider that these symptoms were related to his brucellosis, as the brucellosis had occurred two years before these symptoms developed. One can only speculate how he or his physician might have interpreted these symptoms had the time relationship between their development and his acute brucellosis been closer.

PATIENT 10.—This 33-year-old married man in the chronic-recovered group developed acute brucellosis in 1953. He recovered rapidly, was discharged to home in two weeks, and felt well except for continued moderately severe "weakness." However, over the next year and one-half the patient continued to have recurrent episodes of headache, fatigue, and sometimes insomnia but no fever. The patient regarded these symptoms as evidence of recurrent "brucellosis," and he was twice hospitalized and treated with antibiotics. In the last two years he has been relatively free of symptoms except for occasional periods of "sluggishness."

This patient was rather ingratiating in his manner and affected an air of exaggerated nonchalance. During the interviews it became apparent that he was an accident-prone rather dependent person, with some tendency to be histrionic and to remain oblivious to emotional problems encountered in his living.

He was reared in a large western city and was the seventh of eight children. His mother was described as a very dominating rather harshly punitive parent, and his earliest memory was that of receiving a beating. His father, a comparatively gentle and quiet person, died when the patient was 12 years old.

The patient had been involved in many accidents on different occasions, resulting in a number of fractures. When he was a youth, one of these accidents had been followed by a prolonged period during which he remained partially disabled; on that occasion his disability was dramatically cured one day when he received a fright.

The patient's first marriage ended in divorce. About two years later he contracted brucellosis, and during the year after his acute illness a close relative died. It was in close temporal association with this death that the patient experienced an exacerbation of fatigue and insomnia and was treated with antibiotics. One year later he remarried. There was evidence that he had ambivalent feelings about the prospective marriage, and approximately two months before the wedding date he had another recurrence of subjective symptoms, necessitating a third hospitalization. Since the second marriage the patient had been relatively free of symptoms.

PATIENT 14.—This 35-year-old single man in the chronic-recovered group was employed in a professional capacity at the time he developed acute brucellosis. After recovery from the acute phase of the infection he continued to have symptoms of fatigue and depression. A few years earlier the patient had been persuaded to begin graduate work in chemistry in an eastern university because his family felt that this was best for him. He stated that he bore them no ill feelings and resolved to give it a try. However, he soon found that he was inexplicably unable to apply himself to his studies. His grades were barely passing from the start. He became discouraged and began to drink. To make matters worse, his mother, to whom he felt close, became ill during his first year in graduate school and died at about the time that he finally failed and left school. Shortly thereafter he entered the Army.

At this point the patient became subject to frequent periods of severe guilt feelings and depression, which usually ended in heavy drinking. These symptoms were in full swing when he contracted brucellosis and continued after the acute illness, with fatigue a more prominent symptom than before. The patient noted that his fatigue and depression seemed to wax and wane together.

Approximately three years after his acute infection, the patient's father died suddenly and unexpectedly. About two or three weeks after his father's death, the patient became reconverted in an active zealous way to his family's Protestant faith and joined Alcoholics Anonymous. Since that time he has continued to be active in both his religion and A. A. and has had no further difficulty with drinking, depression, or "chronic brucellosis."

PATIENT 21.—This 51-year-old white man in the chronic-symptomatic group contracted acute brucellosis in 1951. He was hospitalized and treated with antibiotics, and his acute symptoms subsided after several weeks. About three weeks after discharge, the patient developed pain in one hip and left testicular swelling. He was rehospitalized; the testicular swelling disappeared, and again the patient was discharged. Since that time he had been troubled with severe chronic fatigue, low-back and hip aching, other more vaguely described muscular aches, and intermittent impotence. Approximately four years after the onset of this illness, the patient was briefly ill with acute tularemia; it was of interest that the patient's symptoms of "chronic brucellosis" continued essentially unchanged after recovery from tularemia, and both he and his physician considered him to be completely recovered from the latter.

This patient was the first of 12 children, 2 of whom died in infancy. Referring to their state of poverty, the patient described the conditions of his childhood as "bad, bad, bad." He left school in the fourth grade in order to work and had been employed in one job or another thereafter. In his youth, the patient was a fairly aggressive boy with a "temper." In early adulthood he became involved in two accidents, both resulting in head injuries without apparent residual damage. In the second accident he received a near-fatal wound, and he stated that ever since that time he had consistently controlled his temper by walking away from a situation which might be provoking. His emotional control was reinforced by a rather marked tendency to dismiss from his conscious attention any personal problem. He took pride in his ability never to "worry" about anything.

He married at age 22. Several years prior to the onset of brucellosis, his first child died a few days after birth. During his hospitalization with brucellosis his wife delivered their second child, after which he felt that his wife changed her attitude toward him rather markedly in that she became distant and rejecting. Concomitant with the development of this and other marital complications, the patient's father became ill with the first of a series of strokes which ended fatally some three years later. In addition, the patient's aging mother developed a progressive illness, descriptively resembling senile dementia. He has, in this setting, felt intermittently depressed and fatigued and has attempted to achieve some respite through drinking.

PATIENT 23.—This 34-year-old chemical engineer in the chronic-symptomatic group developed brucellosis in 1952. His initial symptoms consisted principally of severe headache, fever, and fatigue. The latter persisted after hospitalization and treatment with antibiotics for about a year, after which the patient gradually improved. The main symptom that continued was weakness.

This patient was reared in an emotionally cold, strict, and poverty-stricken home. He had always been a socially isolated person who preferred various intellectual activities which did not require the company of others. He was shy, inhibited, and self-conscious about his appearance.

Prior to and during his illness the patient considered himself to be in an extraordinarily troublesome situation in which he felt rejected and deprecated by certain members of his family and, indeed, wondered if he had a friend in the world. In this setting, he contracted brucellosis and accepted the diagnosis with a conscious sense of vindication and relief. It was of interest that the patient's symptomatic improvement paralleled partial resolution of his complicated family problem and that his remaining symptom was similar to that with which an aged relative, for whom he felt considerable responsibility, was afflicted.

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Observations on the Diuretic Effect of Chlorothiazide

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Chlorothiazide * (6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide) has been shown to be a potent diuretic substance when given either orally or parenterally.[1-4] Its major effect as a diuretic consists of increasing renal excretion of sodium and chloride, presumably by a decrease in tubular reabsorption, with a secondary loss of water. In vitro chlorothiazide has mild carbonic-anhydrase-inhibition action (approximately 10 times that of sulfanilamide and 1/25 that of acetazolamide [Diamox]); however, this effect has not been implicated as playing a significant role in diuresis in vivo.[1,5] This drug was used in the present study to evaluate its possible mode of action and its effectiveness as a diuretic.

Methods and Materials

This study was divided into two parts: (1) changes in cardiac and renal hemodynamics and in water and electrolyte excretion following intravenous chlorothiazide, and (2) effectiveness of oral chlorothiazide in patients with edema, as evidenced by diuresis and by the changes in electrolyte excretion.

For the first part of the study, eight patients—five with congestive heart failure caused by rheumatic valvular disease, chronic lung disease, hypertensive cardiovascular disease, and coronary artery disease and three normal volunteers—served as subjects. In two normal subjects and in one patient with congestive heart failure, pulmonary and femoral artery pressures were obtained, and cardiac output was determined with use of the Fick principle twice before and twice during the hour (at 20 and 50 minutes) following the intravenous injection of chlorothiazide (3 mg. per kilogram). In all eight subjects, the following additional determinations were performed at approximately 15-minute intervals for one hour before and after the same dose of intravenous chlorothiazide: $C_{In.}$ and C_{PAH}, urine minute volume and pH, and serum and urine concentrations of sodium, potassium, chloride, and carbon dioxide (expressed as milliequivalents per minute). Sodium and potassium were determined with a Beckman flame photometer, and pH was measured by means of a Cambridge glass electrode. Chlorides were analyzed by the method of Schales and Schales.[8] Renal clearance values were obtained by Smith's method, as given by Goldring and Chasis,[6] with the previously reported modification.[7]

For the second part of the study, 36 patients with edema of various etiologies were studied, including 32 patients with congestive heart failure, 3 with Laennec's cirrhosis and ascites, and 1 with estrogen-induced edema (given for carcinoma of the prostate). Twelve of these patients were ambulatory. All of the "congestive failure" patients were receiving a maintenance dosage of digitalis and a diet containing 500 mg. of sodium. Of the hospitalized patients all had recorded daily weights and 24-hour urine volumes. Urine and serum electrolytes were determined daily before and during a five-day treatment period. In 2 subjects determinations of arterial pH, arterial carbon dioxide, and oxygen tensions were obtained before and after 24 hours of oral chlorothiazide and on the fifth day of therapy. After two to five days of stabilization, 2 gm. of oral chlorothiazide were given daily in divided doses every six hours. At the end of the control period, a few subjects continued to excrete sodium in the urine slightly in excess of the 500 mg. in the daily diet prior to the institution of chlorothiazide.

Results

Part I.—Clearance values for inulin and PAH decreased slightly but significantly in all but one of the eight subjects after intravenous injections of chlorothiazide. The mean decrease in $C_{In.}$ was 19 cc. per minute, or 15%, and the mean decrease in C_{PAH} was 78 cc. per minute, or 14% (Table 1).

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* "Diuril," Merck Sharp & Dohme.

TABLE 1.—*Renal Clearances Before and After Chlorothiazide, Three Milligrams per Kilogram, Intravenously* *

Patient	$C_{in.}$ † Before	$C_{in.}$ † After 1 Hr.	$C_{in.}$ † d‖	C_{PAH} ‡ Before	C_{PAH} ‡ After 1 Hr.	C_{PAH} ‡ d‖
1	107	98	9	277	235	42
2	107	93	14	226	198	72
3	85	80	5	250	259	+9
4	43	37	6	105	99	6
5	105	92	13	420	340	80
6§	143	119	24	760	562	198
7§	119	86	33	407	370	37
8§	153	121	32	745	642	106

* Changes in clearances of insulin ($C_{in.}$) and C_{PAH} during 1 hr. following intravenous chlorothiazide, 3 mg/kg, expressed as the mean decrease in ml/min. and % of control value.
† Mean=19 cc/min., or 15% decrease. P=0.01.
‡ Mean=78 cc/min., or 14% decrease. P=0.02.
‖ d indicates difference in % of control value.
§ Normal volunteers.

There were no significant changes in pulmonary artery pressure, femoral artery pressure, cardiac output, or stroke volume in the three subjects in which these were determined during the one hour following intravenous administration of chlorothiazide (Fig. 1).

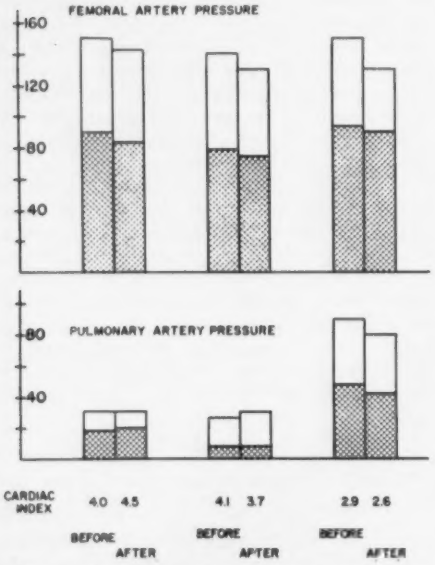

Fig. 1.—Pulmonary artery, femoral artery pressures, and cardiac index before and after administration of intravenous chlorothiazide, 3 mg. per kilogram. (Shaded area indicates diastolic pressures.)

In the face of the slight decrease in glomerular filtration rate and in renal plasma flow, urine excretion of sodium, chloride, potassium, and bicarbonate increased in all eight subjects after the infusion. Excretion of sodium and chloride was enhanced to an approximately equal degree, and in most subjects sizable increases in urine potassium and bicarbonate also occurred. The mean increase in each of these is shown in Table 2, expressed in milliequivalents per minute increase during the one-hour period following intravenous administration of chlorothiazide. There was no change in serum sodium, chloride, potassium, or carbon dioxide.

TABLE 2.—*Urine Electrolyte Excretion After Chlorothiazide, Three Milligrams per Kilogram, Intravenously, in Three Normal Subjects and Five Patients with Congestive Heart Failure* *

Δ	Mean Increase, MEq/Min.	Increase, %	P
Na	0.256	133	0.01
Cl	0.229	125	0.01
K	0.066	68	0.02
CO_2	0.164	200	0.02
pH	1.080	17	0.01

* Absolute change in urine electrolytes during the first hour following intravenous chlorothiazide, 3 mg/kg. The increase is also expressed as a percentage of control values.

Part II.—Nineteen of the twenty hospitalized patients with congestive heart failure responded favorably with loss of weight, decrease in edema, and increase in urine volume and in excretion of sodium, chloride, and, to less degree, potassium. The increase in urine electrolytes was in excess of the increase in urine volume, thus producing an increased concentration of urine electrolytes. The pattern of response is shown in Figure 2 in a patient who had ceased to respond to parenteral mercurial diuretics. The principal increase in sodium and chloride occurred in the first three days of therapy, with declining excretion for the remaining two days. Following the withdrawal of chlorothiazide there was an apparent "rebound" effect, with urinary excretion of sodium and chloride becoming

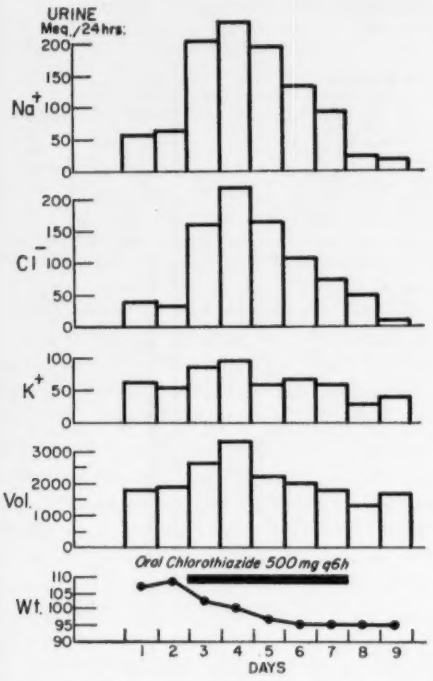

Fig. 2.—Pattern of clinical response to 2 gm. daily of oral chlorothiazide in a patient with hypertensive cardiovascular disease and chronic congestive failure, who was refractory to combinations of ammonium chloride, acetazolamide and meralluride.

significantly less than during base-line stabilization before administration of chlorothiazide. This effect was documented to exist for two to three days after cessation of therapy in all of our subjects in whom detailed electrolyte-excretion studies were carried out. This was attributed to relative depletion of these electrolytes at the end of the therapy period. In the patient of Figure 2, retention of sodium and chloride was still in effect during 27 days immediately following the first five-day course of chlorothiazide; another patient was shown to have this effect for 10 days. Both patients had regained their weight and edema during these periods and had a prompt and equally dramatic response to a second course of oral chlorothiazide. There were two other patients in this group who had ceased to respond to other diuretics (mercurials, acetazolamide, ammonium chloride) but had a good response to chlorothiazide. In the 19 patients who improved in this group, all but 6 had reached their "dry weight" by the end of the five-day treatment period. Table 3 shows the mean increase in urinary electrolyte excretion, expressed in fold increase per 24-hour period, and the mean decrease in weight. There was an increase in sodium of 96 mEq/24 hours ($\pm\sigma$ 44.8, σm 12, $p=0.01$) and in potassium of 27 mEq/24 hours ($\pm$16.8, σm 4.5, $p=0.01$). A mean weight decrease of 9.5 lb. occurred during the five-day treatment period. There was no significant change in urinary pH or bicarbonate, in arterial pH, arterial carbon dioxide, or oxygen tension. The only significant serum electrolyte change was a decrease in chloride of 17 mEq. in one patient. There was a mean decrease of only 8 mEq. per liter in the 20 subjects.

Of the 12 outpatients with congestive heart failure treated with oral chlorothiazide for prolonged periods on maintenance therapy, 8 had been receiving injections of meralluride (Mercuhydrin) twice weekly; 2 had been given parenteral mercurials intermittently to control edema, and 2 had not received previous diuretic therapy. Eleven responded with weight loss and decrease in edema. It was possible to discontinue mercurial diuretics entirely in 8 and maintain this improvement for one to three months. One patient did not respond but became worse, with a 2 lb. weight gain while on chlorothiazide. She also failed to have diuresis with a vigorous regimen of other diuretics. This patient showed an inulin clearance of 43 cc. per minute and a PAH clearance of 105 cc. per minute, thus demonstrating a severe decrease in renal function, presumably accounting for the lack of diuresis. No serum electrolyte depletions were noted in the outpatients, even though treatment was maintained for three months at this rather high dosage.

All three of the patients with Laennec's cirrhosis, ascites, and edema had a favorable response, with a mean weight loss of 8 lb. during the five-day treatment period

TABLE 3.—*Hospitalized Patients with Congestive Heart Failure Treated with Chlorothiazide Two Grams per Day, Orally* *

Patient	Diagnosis	Age	Days of Therapy	Wt. Loss, Lb.	Fold Increase in Urine				Urine Change		Arterial Change		Serum Electrolyte Change, Dec. Cl-MEq.	Changes in Endogenous Creatinine Clearance
					Vol.	Na	Cl	K	pH	$BHCO_3$	pH	P_{CO_2}		
4	RHD	48	5	4	1.2	2.2	1.4	1.5	None	None	None	None	10	No sign. chg.
9	ASHD	62	5	6	1.2	1.7	1.7	1.4	None	None	None	None	7	No sign. chg.
10	Cor. pul.	72	5	5	1.1	2.1	1.7	1.6	None	None			9	No sign. chg.
11	HCVD	60	5	13	1.2	2.9	4.1	1.3	None	None			None	No sign. chg.
12 †	RHD	49	5	6	1.2	5.3	1.2	1.3	None	None			None	Dec. from
11	HCVD	60	5	9	1.5	119.0	13.3	1.5					None	85-75 cc/min.
12	ASHD	68	5	7	1.1	1.0	1.2	1 1					10	
13	HCVD	62	5	8	2.0	2.2	2.3	1.6					None	
14	Cor. pul.	63	5	13	3.3	47.0	18.0	2.1					17	
15	ASHD	65	5	13	4.4	5.7	8.6	5.3					10	
15	ASHD	64	5	7	1.3	2.6	2.5	1.5					6	
12 †	Cor. pul.	56	5	8	1.2	5.1	3.5	1.6					12	
													1	
16	RHD	53	5	23	6.4	13.0	10.0	1.6					7	
													1	
17	HCVD	42	5	3	0	4.0	3.2	1.6					9	
18 †	ASHD	87	29	19										
19 †	Cor. pul.	57	16	4										
20 †	ASHD	77	15	13										
2 †	Cor. pul.	55	11	23										
12	ASHD	65	4	7										
4 †	RHD	49	5	0										
			P values		0.2	0.01	0.01	0.01						

* Response of hospitalized patients with congestive heart failure. Increase in 24 hr. urine electrolytes is expressed in fold increase over control values.
† Patients with some edema remaining after 5 days of oral chlorothiazide.

TABLE 4.—*Laennec's Cirrhosis with Edema and Ascites Treated with Chlorothiazide, Two Grams per Day, Orally, for a Five-Day Period* *

Patient	5-Day Wt. Loss, Lb.	Fold Increase in Urine				Serum Electrolytes	Edema Remaining	Improvement
		Vol.	Na	Cl	K			
21	7	2.6	3.6	2.1	4.5	N	3+	Slight
22	6	2.5	4.7	8.1	1.9	N	3+	Slight
23	10					N	2+	Moderate

* Response of hospitalized patients with Laennec's cirrhosis to 2 gm. daily of oral chlorothiazide. Increase in urine electrolyte excretion is expressed as fold increase per 24 hr. over the control values.

with a slight decrease in edema. The electrolyte-excretion pattern was the same as in the patients with congestive heart failure, but the degree of response was slightly less. Table 4 shows the electrolyte excretion expressed in fold increase over base-line values. One of these patients had an increase in symptoms of "impending hepatic coma" on two separate occasions when given oral chlorothiazide. He showed improvement on each occasion when this drug was discontinued. There was no significant change in serum electrolytes.

The one patient with estrogen-induced edema responded in a similar manner on two separate occasions. There was a decrease in edema, a weight loss of 8 and 9 lb., respectively, and an increase in excretion of sodium, chloride, and potassium.

Comment

As a diuretic agent, chlorothiazide appears effective and may, in fact, be considered second only to the organomercurials. It has the practical advantage of being as effective orally as parenterally. Its mechanism of action is different from that of other compounds. A mild carbonic-anhydrase inhibition can be shown in man if sufficiently high amounts are given (doses in excess of that required for effective diuresis). This, however, is not its mode of effective action. The pattern of urine electrolyte excretion is similar to that following administration of mercurial compounds, but it differs from these by its ability to induce dramatic natruresis, chloruresis, and diuresis in some patients with mercurial refractory edema and by the absence of a demonstrable effect of hyperchloremia, acidosis, or alkalosis on the resultant diuresis.

This drug is effective in reducing edema due to congestive heart failure, cirrhosis, hormone therapy (estrogens and adrenal cortical hormones), nephrotic syndrome, and chronic renal insufficiency.[1-4] Continuous administration of chlorothiazide apparently does not produce refractoriness, the gradually declining response paralleling the disappearance of edema. The lack of refractoriness can be easily demonstrated by renal excretion of an increased ingestion of sodium chloride by patients with a declining response. An equal response also occurs with a second course of therapy when the patient has been allowed to reaccumulate his edema.

Our studies indicate little if any effect of this agent on cardiac output, glomerular filtration rate, and renal plasma flow. There is a slight but significant decrease in both glomerular filtration rate (GFR) and renal plasma flow (RPF), as measured by inulin and PAH clearances, which might be considered detrimental under some circumstances. There were, however, no significant changes in the endogenous creatinine clearances in several subjects given 2 gm. daily of oral chlorothiazide.

Extremely few toxic manifestations have been observed with chlorothiazide therapy. Anorexia, nausea, and vomiting have occurred infrequently and are promptly corrected by cessation of therapy. During short courses (five days) significant serum electrolyte changes did not occur in our patients. However, hypokalemia and hypo-

chloremia requiring replacement therapy have been observed by others after prolonged chlorothiazide administration. The use of supplemental potassium chloride has been reported to prevent these abnormalities. Hepatic coma can be induced in patients with severe impairment of liver functions. The mechanism responsible for this is not clear. In our series no untoward reactions occurred.

The possible occurrence of ectopic foci in digitalized patients receiving chlorothiazide medication should be mentioned. We have observed six patients in whom ventricular premature foci occurred which seemed to be related to chlorothiazide therapy, disappeared when the drug was discontinued, and reappeared when treatment was reinstituted. All patients had severe coronary artery disease, and two died suddenly while on therapy. In all subjects serum potassium levels were normal at the time the irregularities occurred; one subject was on supplementary oral potassium, and in all, urine potassium excretion was no higher than in other subjects. These findings may be entirely fortuitous.

Summary

Chlorothiazide, a nonmercurial diuretic, was administered to 44 subjects. Detailed blood and urine electrolyte determinations were obtained in all, and renal and cardiac hemolynamic studies were carried out in eight.

Associated with profound water diuresis there occurred an increase in sodium and chloride excretion in the urine, which was independent of the cause of the edema and was generally followed by a period of sodium and chloride retention upon cessation of therapy. There was no demonstrable serum electrolyte depletion.

Cardiac function and vascular pressures were unaltered in three subjects receiving intravenous medication. There was a slight decrease in renal plasma flow and in glomerular filtration rate in eight patients following the intravenous administration of 3 mg. per kilogram of chlorothiazide.

The drug is well tolerated, but the occurrence of cardiac irregularities during therapy in some digitalized subjects needs further elucidation.

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A Clinicopathological Study of Acute Myocardial Infarction and the Role of Anticoagulation Therapy

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Although it has been 10 years since Wright, Marple, and Beck [1] first suggested the use of anticoagulants in acute myocardial infarctions, there remains confusion and uncertainty in the minds of many clinicians as to the role of this form of therapy. Most clinical studies have reported a definite decrease in both morbidity and mortality in patients receiving anticoagulants as compared with control groups. Even so there remains a conflict in the literature as to which patients should and should not be treated with anticoagulants, what may be expected in the way of preventing thromboembolic complications, and how soon after the acute myocardial infarction the anticoagulants should be initiated if they are to be effective.

The present study was initiated to answer these questions. However, it quickly became evident that for this study to be valid numerous other factors would have to be considered and compared between the control and treated groups. Hence this work was enlarged from simply a survey of anticoagulation in acute myocardial infarction to a study of acute myocardial infarctions in general.

Method

The data presented in this thesis were obtained through a review of hospital charts to collect all the cases with acute myocardial infarctions presenting at The Ohio State University Hospital from January, 1942, through December, 1957. This 16-year period was then divided into two groups. During the first eight-year period, from 1942 through 1949, almost no anticoagulants were used, while during the second period anticoagulation therapy was almost routine. The purpose of this division was to determine any difference that there might have been in the ancillary forms of treatment of an acute myocardial infarction as seen at our institution over these 16 years. The first period would serve as a general control for the second period. Over 1,100 charts were read during this survey, and 623 were used in formulating these data. Only patients having unequivocal electrocardiographic evidence of an acute myocardial infarction or cases having autopsy evidence of an acute myocardial infarction after clinical evaluation were considered valid for this study. This includes patients having one or multiple infarctions but does not include any cases in which the patient either was dead on arrival at the hospital or died before adequate clinical evaluation had been obtained. That is, the diagnosis had to be entertained and the initial stages of therapy were instituted on all patients included in this study.

In any clinical survey such as this, in which many circumstances, complicating factors, and intangibles must be considered, evaluated, and set down in concrete terms, there must necessarily be shaded decisions and certain assumptions made during the study. As we realized this full well and wished to minimize subjective variables in judgment, all of the charts were read by one person, and all of the values assigned and decisions reached were made by that same person. The specific criteria used in classifying the various categories during this study will be noted under the individual headings.

Incidence of Various Associated Factors

Age.—In Bean's [2] thorough clinical appraisal of myocardial infarctions in 300 patients, the average age of the males was 60.1 years and the average female age was 61.7 years. The greatest percentage of his patients were in the seventh decade, with the sixth and eighth decades being equal. Keil and McVay [3] studied 519 patients, with emphasis on the comparison in white and Negro groups, and reported an average age of 62.0 years for the white man, 66.5 years for the white woman, 60.6 years for the Negro man, and 56.0 years for the Negro woman. Others [4-6] have reported figures of

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TABLE 1.—*Age-Sex-Race Incidence*

Age, Yr.	White		Negro		Total
	Male	Female	Male	Female	
<30	0	0	1	0	1
31–40	10	2	5	0	17
41–50	83	8	6	8	105
51–60	119	31	7	8	165
61–70	110	61	6	7	184
>70	88	53	6	4	151
Totals	410 (66%)	155 (24%)	31 (5%)	27 (5%)	623

54.0 to 62.4 years as an over-all average. Most clinicians agree that 80% to 85% of the infarctions occur in the 40- to 70-year age group, with the peak in the seventh decade. Men have infarctions about three years before women, except for the Negro women, who have infarctions at a much earlier age than white women or even white men.

The average age for white men in our study was 59.5 years; white women, 64.6 years; Negro men, 54 years, and Negro women, 57 years. The youngest patient was a 29-year-old Negro man, and the oldest was an 86-year-old white man. There was close agreement among the sixth-, seventh-, and eighth-decade age groups, with 26%, 30%, and 24% of the patients falling into these respective groups.

Table 1 shows the breakdown by age, sex, and race.

Sex.—The usually reported incidence of infarctions in men as compared to women has been 3:1. Bean [2] reported a 2.3:1 ratio. Keil and McVay [3] reported a 2.9:1 ratio in white patients and a 1.2:1 ratio in Negroes. Others [5,6] have reported 2.2:1 to 3.4:1. The present study shows a 2.6:1 ratio in white patients and a 1.1:1 ratio in Negroes. Again the reason for the high incidence in Negro women is unexplained.

Mortality.—The over-all mortality for acute myocardial infarctions has been reported as 21.8% to 60%.[3-6] The mortality in the present study, which includes primary and multiple infarction patients, was 38% in the men and 45% in the women (Table 2).

Diabetes.—There are two ways to compare the clinical incidence of diabetes and myocardial infarction. One method would be to determine the number of patients having diabetes in a series of myocardial infarctions. The other would be to follow a number of diabetics for several years to determine the incidence of myocardial infarctions occurring in this group. Studies utilizing the first method [2,5-7] have reported a diabetes incidence of 11% to 20% in patients with acute myocardial infarction. Keil and McVay [3] reported an incidence of 3.5% in men and 15.0% in women. Studies [8-10] utilizing the second method have indicated that 33% to 50% of all diabetics have myocardial infarctions. The mortality of patients with diabetes is higher than in a nondiabetic group. Mintz and Katz [5] report a mortality of 27.8% in men with diabetes, as compared to 18% without. Women with diabetes have a 36.7% mortality, as compared to 29% in the nondiabetic group.

In the present series 10.6% of the men and 24.1% of the women had diabetes, for an over-all incidence of 14.5%. A comparison of the mortality showed that 35% of nondiabetic men died, whereas 60% of the diabetic men died. Among the women, 43% of the nondiabetic women died,

TABLE 2.—*Mortality*

	Men		Women	
	No.	%	No.	%
Lived	275	62	100	55
Died	166	38	82	45
Total	441		182	

TABLE 3.—*Diabetes*

Duration of Diabetes, Yr.	Men		Women	
	Lived	Died	Lived	Died
Never	256	138	79	59
<5	14	16	14	11
5–10	1	9	4	7
10–20	4	2	2	4
>20	0	1	1	1
Total with diabetes	19	28	21	23

TABLE 4.—*Hypertension*

Duration of Hypertension, Yr.	Men		Women	
	Lived	Died	Lived	Died
Never	165	108	49	45
Unknown	57	31	14	10
<1	4	1	1	3
1-3	23	12	9	7
4-6	12	7	11	9
>6	15	7	16	8
Total with hypertension	111	58	51	37

TABLE 5.—*Angina Pectoris and Premonitory Pain*

Duration of Symptoms	Men		Women	
	Lived	Died	Lived	Died
Never	143	97	58	47
1 wk	22	7	8	6
1-2 wk	12	5	5	6
2-4 wk	12	4	6	2
1-6 mo	26	20	5	6
>6 mo	60	33	18	15
Total with symptoms	132	69	42	35

whereas 52% of the diabetic women died.

The complete breakdown, including the duration of diabetes in the patients with acute myocardial infarction, is presented in Table 3.

Hypertension.—The incidence of hypertension has been reported as occurring in 27% to 63% of patients experiencing acute myocardial infarction.[2,4-6,11] Almost every study has shown a proportional sex ratio, and most have agreed that there is no relationship between hypertension and mortality. In the present series hypertension is defined as a diastolic pressure in excess of 95 mm. of mercury. Thirty-eight per cent of the men and forty-eight per cent of the women had hypertension. The mortality in men was 35% with hypertension and 40% in patients without hypertension. Among the women, 42% with hypertension died, while 47% of the control group died.

Table 4 contains the specific details, including the duration of hypertension before the infarction occurred.

Angina Pectoris.—The usual incidence of angina pectoris occurring in patients before developing a myocardial infarction has been quoted [2,4] as 33% to 37%. However, when the so-called "premonitory" pain, that is, a severer, more unrelenting angina, or angina of recent onset occurring a few days to a few weeks before an acute myocardial infarction, is included, the figure quoted is 50% to 73%.[5,12-14] Keil and McVay [8] have indicated the incidence of angina prior to myocardial infarction to be 48% in white men, 57% in white women, 32% in Negro men, and 26% in Negro women.

The present study included patients with both prolonged angina and "premonitory" coronary pain. Forty-eight per cent of the men and forty-three per cent of the women had angina. The mortality among the men with angina was 34%, as compared to 40% in the patients without previous pain. The mortality was 45% in the women, both with and without angina.

Table 5 includes the patients with angina and premonitory pain and indicates the duration of the cardiac pain prior to the acute myocardial infarction.

Cardiac Failure.—Reports in the literature [4-6] have indicated that cardiac failure occurs either before or during the early phase of an acute myocardial infarction in 46% to 51% of patients. In the present study 21% of the men and 35% of the women had a history of cardiac failure prior

TABLE 6.—*Cardiac Failure*

Duration of Symptoms	Men		Women	
	Lived	Died	Lived	Died
Never	236	113	72	45
1 wk	3	5	2	1
1-4 wk	2	5	1	4
1-6 mo	7	8	5	8
>6 mo	27	35	20	24
Total with symptoms	39	53	28	37

TABLE 7.—*Previous Illness*

Type	Men		Women	
	Lived	Died	Lived	Died
Thyroid	13	5	11	5
Syphilis	11	4	5	3
Rheumatic heart disease	2	4	1	0

to the onset of their acute myocardial infarction. Another 17.5% of the patients developed cardiac failure either at the time of or shortly after admission to the hospital. This means that a total of 265 patients, or 42.5%, had cardiac failure either before the onset or during the acute phase of the infarction. A comparison of mortality shows that men with cardiac failure had a 57% mortality, while those without cardiac failure had only a 32% mortality. Among the women with cardiac failure, 58% died, while only 38% of the women without cardiac failure died (Table 6).

Previous Illness.—The incidence of other possible contributing illnesses as determined in this study is as follows:

Thyroid: Both hyperthyroidism and hypothyroidism occurred in 4.1% of the men and 8.9% of the women.

Syphilis: Syphilis occurred in 3.4% of the men and 4.4% of the women.

Rheumatic Heart Disease: This was associated with acute myocardial infarction in 1.4% of the men and 0.5% of the women (Table 7).

Therapy

To determine truly the efficacy of anticoagulant therapy, the selection of patients in the control and treated groups should be equitable and the over-all care of the patients should be similar. Since most of the patients before 1950 did not receive anticoagulants and the majority of the patients after 1950 did receive them, the entire series was divided into these two eight-year periods. The purpose of this division was to determine whether or not the physicians handling the patients during these two periods had essentially the same philosophy concerning bed rest, oxygen, narcotics, and sedation. Some criticism has been raised concerning the decreased morbidity and mortality in patients who have received anticoagulants in that these other measures may also have been changed. Hence the question: Is anticoagulation alone responsible for improving morbidity and mortality in patients with acute myocardial infarction?

Bed Rest.—All patients, whether they lived or died, were included in this section. Therefore there will be a disproportionately larger number of persons having less than four days of bed rest than one would expect. However, this should be the same for both groups if the division is equal. Patients were considered to be on bed rest until they were allowed up in a chair. This criterion may draw criticism in some areas, but at Ohio State the plan of armchair treatment of the myocardial infarction has not been popular and only infrequently has been used. Usually when a patient is allowed up in a chair it means the start of ambulation, unlike the true concept of armchair management. On the other hand, allowing a patient the use of a bedside commode is frequently done while the patient is on complete bed rest in all other ways.

The data for this section were obtained for the most part from the doctors' order sheets in order to note when after admission the patient was allowed up in a chair. This usually followed bedside dangling by several days.

Table 8 demonstrates how remarkably close the two groups are.

Oxygen.—The collection of data on the use of oxygen was very difficult to obtain. Very often the order to discontinue oxygen is verbal and no written record is available. When oxygen therapy was initiated and no order could be found to discontinue its use, the nurses' notes and the treatment sheets were perused to determine when the oxygen may have been stopped. Usually the duration of treatment could be determined with accuracy. Occasionally the oxygen would be

TABLE 8.—*Bed Rest*

	Before 1950		After 1950	
Duration, Days	No.	%	No.	%
<4	58	30	117	27
5-7	21	10	39	9
8-14	47	24	94	22
15-21	29	15	96	22
>22	39	21	86	20
Total	194		432	

TABLE 9.—*Oxygen*

Duration, Days	Before 1950 No.	Before 1950 %	After 1950 No.	After 1950 %
None	104	54	158	36
1	31	16	116	27
2	13	7	43	10
3	13	7	41	10
4	11	6	29	7
5	1	1	11	2
6	3	1	10	2
7	5	3	8	2
8	9	5	16	4
Total	190		432	

stopped and then restarted at a later date as complications arose. In these cases, the two periods were added and the total number of days of oxygen therapy was reported.

Table 9 contains the data for this study. For the most part the figures are almost identical, but it will be noted that since 1950 more patients were started on oxygen initially and then stopped during the first day. This may reflect the increasingly widespread use of oxygen without awaiting the evidence of cyanosis, cardiac failure, shock, prolonged pain, or the usual indications for oxygen therapy.

Narcotics and Sedation.—The use of morphine for the patient with acute myocardial infarction is one of the more important aspects of treatment. No drug is more effective in relieving the pain and alleviating the anxiety occurring in the early stages of the infarction. The accomplishment of these objectives should be paramount in the physician's mind. There has been a great difference in the degree of use of morphine sulfate before and since 1950. The latter period showed a marked increase in the amount and duration of morphine given to patients. Whether this means a sicker group of patients with more pain or a change in philosophy to give patients narcotics with less indication or by routine order is not known.

TABLE 10.—*Morphine*

Amount	Before 1950 No.	Before 1950 %	After 1950 No.	After 1950 %
Low	80	42	114	26
Moderate	83	43	281	65
High	28	15	37	9

It will be noted in Table 10 that the number of patients receiving high doses of morphine remains about the same, whereas the group receiving moderate amounts has increased by 22% and the group receiving low amounts has decreased by 16% since 1950.

The criteria for these divisions were as follows:

Low: The patient received either no morphine or only one dose at the time of admission.

Moderate: The patient required several doses of morphine at irregular intervals.

High: The patient received large doses of morphine per routine order for prolonged periods of time.

General Narcotics: The criteria for classification in the general narcotics group (Table 11) were similar to those described for morphine. All the various narcotics administered were considered under this heading, except morphine. Naturally meperidine (Demerol) was by far the most prevalent of the general narcotics used. Again the proportion of patients requiring high dosage is almost identical, whereas the group receiving moderate doses has been increased by 17% and the group using little or no narcotics has been decreased by 19% since 1950.

Sedation: The over-all use of sedation, including both daytime sedation with bar-

TABLE 11.—*General Narcotics*

Amount	Before 1950 No.	Before 1950 %	After 1950 No.	After 1950 %
Low	140	73	232	54
Moderate	40	21	166	38
High	11	6	34	8

TABLE 12.—*Sedation*

Amount	Before 1950 No.	Before 1950 %	After 1950 No.	After 1950 %
Low	145	76	317	73
Moderate	34	18	99	23
High	12	6	16	4

biturates and nighttime sedation, has remained constant over the 16-year period. Table 12 indicates that very little routine or daytime sedation has been used in the treatment of acute myocardial infarction.

Anticoagulation.—The problem of anticoagulation therapy in acute myocardial infarctions has many facets; hence, it is not at all surprising that there is still a great deal of controversy and indecision concerning its use and the evaluation of its benefits. The most comprehensive study to date has been the cooperative study by the Committee for the Evaluation of Anticoagulation in the Treatment of Coronary Thrombosis with Myocardial Infarction, sponsored by the American Heart Association and reported by Wright, Marple, and Beck.[15] The over-all mortality in their 1,031 patients was 23.4% in the control groups and 16.0% in the treated groups. They also reviewed reports from other workers having a total of 2,812 cases and found 14.8% mortality in the patients receiving anticoagulants and 29.5% mortality in the control group.

In the present series, the patients have been divided into three groups: (1) patients who received no anticoagulants, (2) those who received adequate amounts of anticoagulants, and (3) those who received inadequate anticoagulants. Our criteria were similar to those of Wright et al. in that the patients who received adequate anticoagulants were required to have a prothrombin time of 30% or less for 70% of the time for the first three weeks after an acute myocardial infarction. We were a little more stringent in that we included only those patients who had reached therapeutic levels within four days, whereas Wright allowed six days in his series. Our third group consists of patients who received inadequate amounts of anticoagulant. They either died before they reached therapeutic levels, did not reach an adequate level of anticoagulation by the fourth day, or did not maintain less than a 30% prothrombin time for 70% of the time.

In this study 369 patients received no anticoagulants at all. At first glance it may be thought that this group is loaded in that 81 patients, or 22% of the entire group, died during the first 12 hours of hospitalization and could not be given anticoagulants for this reason. However, a comparable number of patients, namely, 75 or 20% of the total, did not die until four or more days after the onset of their infarction. This latter group might have given adequate anticoagulation therapy and yet were purposely not given anticoagulants. Hence, one factor probably balances the other.

There were 108 patients who were inadequately controlled. Eleven of these patients received only one or two doses of anticoagulants and then died. The remainder of these patients were started on anticoagulants, and then either they were seen to be good-risk patients and the anticoagulants were allowed to lapse or else they just could not be controlled at the therapeutic levels.

We had 146 patients who received adequate anticoagulation. This group has an over-all mortality of 17.1%, as compared with 20.4% in the group with poor anticoagulation and 54.5% in the group not receiving anticoagulants, or control.

It will also be noted in Table 13 that these figures have been broken down again into two groups, before and after 1950, to determine whether or not other therapeutic measures might have influenced the mortality rates. There is an amazing correlation in the six subdivisions when compared in this manner. Hence it may be said that our ancillary therapy before and since 1950 has not changed the mortality rates, whereas the addition of anticoagulants has had a profound influence on mortality.

Thromboembolic Complications: The last paragraph indicated a remarkable difference

TABLE 13.—*Anticoagulation*

	Before 1950				After 1950			
	Lived		Died		Lived		Died	
Type	No.	%	No.	%	No.	%	No.	%
None	70	47	79	53	98	45	122	55
Poor	20	80	4	20	66	78	18	22
Good	13	72	5	28	108	84	20	16

in mortality between the group receiving anticoagulants and the group not receiving them. It was also shown that this was probably due solely to the factor of anticoagulation and was not affected by other forms of treatment. If these statements are valid, then there should be a marked difference in the number of thromboembolic complications in the two groups. This was investigated, and the various complications were separated into the categories of peripheral emboli, thrombophlebitis, pulmonary emboli, and mural thrombi as diagnosed clinically and seen at autopsy.

The total incidence of thromboembolic complications, as seen in 321 patients receiving anticoagulation therapy by Gilchrist and Tulloch,[16] was 10.6%. The number of thromboembolic complications in a 128-patient control group, as reported by Bresnick et al.,[17] was 20.3%. The present series had a total of six cases of thromboembolic complications in the patients receiving adequate anticoagulation, for a 4.1% incidence. The group receiving inadequate anticoagulation had 15 cases of thromboembolic complications, for a 13.9% incidence, and the control group had 57 cases of thromboembolic complications, for a 15.5% incidence.

Thrombophlebitis: The incidence of thrombophlebitis in the literature has been reported as occurring in 7% to 9% of persons with acute myocardial infarctions who are not receiving anticoagulants.[18,19] In our series there was little difference in the incidence of thrombophlebitis between the control group and the group receiving anticoagulants. The incidence was 2% in the control group and 3% in the treated group. Only one patient having thrombophlebitis in each of the groups died. Unfortunately, the pathology department does not examine the leg veins beyond the common iliacs except to attempt to express the thrombus through leg massage, and this is done only on patients suspected of having thrombophlebitis. Therefore, our incidence of thrombophlebitis as found at autopsy may be erroneously low (Table 14).

TABLE 14.—*Thrombophlebitis*

Thrombophlebitis	Anticoagulation		
	Good	Poor	Control
None	142	105	364
Clinical	4	3	5
Autopsy	1	1	1
Incidence	3%	3%	2%

Peripheral Emboli: It has been reported that 4% of persons having acute myocardial infarction without anticoagulation therapy have developed peripheral emboli.[19] This is in close agreement with our series in which 4.0% of the control group had peripheral emboli. The patients with adequate anticoagulation had only one episode of peripheral embolization, for a 0.7% incidence. The poorly controlled patients had a 4.6% incidence of peripheral embolization.

In the group receiving adequate anticoagulation, the one patient who had an embolus to his leg also died. In the poorly controlled group, one patient had an embolus to his arm and later died. Two others were presumed to have emboli to their brains. One occurred on the 8th day and the other occurred on the 16th day after the onset of myocardial infarction. One died and was not autopsied, and the other lived with a nondominant stroke. It is impossible to determine whether these cerebrovascular accidents were actually caused by embolization or thrombosis, but since they occurred relatively late in the hospital course we considered these to be emboli. Two other patients among this group were autopsied and were noted to have emboli to their spleens. In the patients not receiving anticoagulants, two of the group had emboli to their arms. Both died later, and the autopsies confirmed the presence of emboli. Two others had emboli to the legs. Both died, but only one was autopsied, and the presence of an embolus was confirmed. Four patients had cerebrovascular accidents, and three of these died. Two were autopsied and were said to have cerebral emboli. Seven other patients had no clinical evidence of peripheral emboli but were noted to have

TABLE 15.—*Peripheral Emboli*

Type	Anticoagulation		
	Good	Poor	Control
None	145	103	354
Arm	0	1	2
Leg	1	0	2
Gastrointestinal	0	0	1
Genitourinary	0	0	5
Central nervous system	0	2	4
Spleen	0	2	1
Total with emboli	1 (0.7%)	5 (4.8%)	15 (4.0%)

TABLE 16.—*Pulmonary Embolism*

Pulmonary Embolism	Anticoagulation		
	Good	Poor	Control
None	145	104	355
Clinical	1	3	9
Autopsy	1	1	9
Total with embolism	1(0.7%)	4(3.8%)	14(3.8%)

emboli at autopsy. Five of these were in the kidney; one, in the spleen, and one, in the gastrointestinal tract (Table 15).

Pulmonary Embolism: The incidence of pulmonary embolism after acute myocardial infarction has been reported as 7% to 29%.[18-22] Gilchrist [18] reported a 14.7% incidence in patients receiving anticoagulation therapy and a 40.5% incidence in a control group. Wright [23] reported an 8% incidence in treated patients and a 23% incidence in his control series. The incidence in the present series is far under these figures. The over-all incidence, clinical plus autopsy, was 0.7% for the group receiving adequate anticoagulants and 3.8% for both the group receiving inadequate anticoagulation and the group receiving none.

Only one patient receiving adequate anticoagulation therapy was diagnosed clinically as having a pulmonary embolus. He died, and at autopsy the diagnosis was confirmed. Three of the patients receiving inadequate anticoagulation were considered to have pulmonary emboli. One died but was not autopsied. One other patient in whom the diagnosis was not considered clinically was noted to have a pulmonary embolus at autopsy. Among the patients not receiving anticoagulants, nine were clinically suspected as having pulmonary emboli. Six died, and four were autopsied, and the clinical impression was confirmed. Five other patients among this group in whom the diagnosis was not suspected clinically were noted to have pulmonary emboli at autopsy.

The source of the pulmonary emboli as determined at autopsy was thrombophlebitis in three cases, right ventricle in one case, and right atrium in one case; the origin could not be determined in six cases. Table 16 summarizes the findings of pulmonary emboli in both clinical and postmortem cases.

Mural Thrombus: The presence or absence of mural thrombi after an acute myocardial infarction is an autopsy determination. One might suspect the presence of a mural thrombus after there is evidence of a pulmonary or peripheral embolus, but the diagnosis can only be presumptive without postmortem examination. In the present study only autopsy material is included in the discussion of mural thrombi.

One of the major questions in clinicians' minds is whether or not anticoagulation has to be started immediately, or whether one might wait two or three days before initiating anticoagulant therapy. The duration of time between the onset of an acute myocardial infarction and death was determined in patients having mural thrombi. This was to discover at what time interval a significant number of mural thrombi would have been formed. These data were not calculated from the time of admission but rather from the time of onset of symptoms. All patients with myocardial evidence of an old infarction were excluded. We found that eight patients had mural thrombi by the third day. An additional nine had mural thrombi by the end of the first week. Since there was a total of 47 mural thrombi found during this study, it is evident that one-sixth of these will have been formed before most anticoagulation has become therapeutic, and if one delays until the third or fourth day, one-third of the mural thrombi will have been formed before therapy is effective.

TABLE 17.—*Mural Thrombus*

Position	Anticoagulation: Good	Anticoagulation: Poor	Control
None	12	7	81
Right ventricle	0	0	2
Left ventricle	1	6	33
Both ventricles	1	1	3
Total with thrombus	2 (14%)	7 (50%)	38 (32%)

The incidence of mural thrombi has been reported [16,23] as occurring in 40.5% to 62.5% of patients in control groups and 31.7% to 38% in patients receiving anticoagulants. In an autopsy study by Glueck et al.,[24] mural thrombi were demonstrated in 23% of patients receiving adequate anticoagulation therapy, 60% in patients receiving inadequate anticoagulation, and 41% of the control group. Our results were quite similar to theirs in that 14% of our patients receiving adequate anticoagulation therapy, 50% of the group receiving inadequate anticoagulation therapy, and 32% of the control group had mural thrombi.

Table 17 contains the breakdown of these figures and indicates the position of the mural thrombus.

To summarize the thromboembolic complications, the total incidence was 5.5% for the patients receiving adequate anticoagulation, 17.6% in the patients receiving inadequate therapy, and 19.5% in those receiving none. The incidence of deaths attributable to thromboembolic complications was 1.4% of the group receiving adequate anticoagulation and 4.9% of the control group.

TABLE 18.—*Thromboembolic Complications*

Type	Anticoagulation: Good	Anticoagulation: Poor	Control
Patients, total	146	108	369
No thromboembol.	140	93	312
Thrombophlebitis	4	3	5
Peripheral emboli	1	5	15
Pulmonary emboli	1	4	14
Mural thrombi	2	7	38
Total incidence	8(5.5%)	19(17.6%)	72(19.5%)
Cause of death	2(1.4%)	4(3.8%)	18(4.9%)

Table 18 contains the total incidence of thromboembolic complications and the mortality resulting from these complications.

Anticoagulation Complications: Of the 146 patients who received adequate anticoagulation there were 6 possible cases of hemorrhage. One patient had severe gastrointestinal hemorrhage and died. One other patient developed blood in his stool on several occasions, and another had gross hematuria while receiving adequate anticoagulation therapy. Three patients developed cerebrovascular accidents while under therapy. One of these patients died but was not autopsied. It is possible that these patients had either emboli or thrombi, but since the stroke occurred while they were receiving adequate anticoagulation they are considered as cases of brain hemorrhage. Two of the autopsied patients had hemopericardium but not of sufficient quantity to have caused cardiac tamponade. Patients on anticoagulant therapy have not had routine stool guaiac tests or routine microscopic examination of the urine, hence many other minor cases of hemorrhage may have gone unnoticed. We consider the incidence of hemorrhage as determined in this study to be 5.4% and the incidence of death due to anticoagulation therapy to be 1.4%.

Myocardial Rupture: Autopsy studies have shown a 7% to 9.5% incidence of rupture in all patients with acute myocardial infarction.[25-27] Studies reported on patients receiving anticoagulants and on control groups have indicated that rupture of the myocardium is twice as frequent in the patients receiving anticoagulation therapy.[28] Waldron et al.[29] included patients with both cardiorrhexis and hemopericardium and showed a 5% incidence in patients not receiving anticoagulants and a 14.1% incidence in treated patients. The cooperative study by Wright, Marple, and Beck [15] showed an incidence of 8.3% in the control group and 19.5% in the treated group. These same studies plus a report on a study of patients in a mental institute [30] have shown that activity, hypertension, and the use of anticoagulants increase the incidence of rup-

ture. Digitalis has not been shown to increase the incidence of rupture.[31] These same studies show that 45% of the patients who have an acute myocardial infarction and later rupture do so in the first three days, 70% in the first week, and 95% by the end of the second week.

Among the autopsied patients in the present study, none of the 14 patients receiving adequate anticoagulation therapy who were autopsied had rupture of the myocardium, but 2 had a hemopericardium. Two of the fourteen patients given inadequate anticoagulants and five of the one hundred nineteen patients not treated who were autopsied had a ruptured myocardium. One of the control patients had a hemopericardium. In combining the incidence of both hemopericardium and myocardial rupture, our figures (Table 19) coincide almost exactly with those of Waldron.[29]

TABLE 19.—*Cardiorrhexis and Hemopericardium*

Type	Anticoagulation		
	Good	Poor	Control
Neither	12	12	113
Cardiorrhexis	0	2	5
Hemopericardium	2	0	1
Total incidence	2 (13.3%)	2 (13.3%)	6 (4.8%)

Good-Risk Patients: One of the major areas of contention in the problem of anticoagulation therapy has been raised by Russek and his group. They feel that some patients who develop an acute myocardial infarction may be better risks than other patients and that the risk entailed in treating these good-risk patients with anticoagulants outweighs the expected benefits. The criterion used for the selection of good-risk patients was an absence of the following conditions: (1) previous myocardial infarction; (2) intractable pain; (3) extreme degree or persistence of shock; (4) significant enlargement of the heart; (5) gallop rhythm; (6) congestive heart failure; (7) atrial fibrillation, auricular flutter, ventricular tachycardia, or intraventricular block; (8) diabetic acidosis, marked obesity, previous pulmonary embolism, varicosities, thrombophlebitis past or present, and other states predisposing to thrombosis. Russek[32-34] feels that about 45% of the patients presenting with an acute myocardial infarction can be placed in the good-risk category and that the mortality in this group is only about 3.5%. The number of deaths preventable by the use of anticoagulants he calculates to be about 1%. When this is compared to the 0.7% to 1.7% of deaths usually reported as resulting from complications in the use of anticoagulants, there is obviously nothing to be gained from using anticoagulants in these patients.

Table 20 presents a summary of Russek's findings.

TABLE 20.—*Good-Risk Patients, After Russek*[32]

	Patients, No.	Mortality, %	Emboli, %
Good risk	285	3.5	0.7
Poor risk	338	70.1	12.4
Total	623	29.6	7.1

There is no doubt that if we were to select patients having the most favorable prognosis we would agree reasonably closely to the criteria of Russek. Unfortunately it is extremely difficult to classify these patients when they are first admitted to the hospital. Gilchrist and Tulloch[16] state the problem very well when they say: "Only in retrospect are there good risk patients with acute myocardial infarction. The illness runs a treacherous and for the most part, an unpredictable course." Halpern et al.[35] reported on 107 clinical cases which his group tried to classify. They had to reverse their decision in 29% of the cases in the first 24 hours. Halpern concluded that it was impossible to determine good- and poor-risk cases clinically when first seen on admission. Russek[34] reports a much smaller number of reversals, but he too advocates watching patients for 48 hours to determine their classification before initiating anticoagulation therapy. We cannot agree that watching the patient for 48 hours is warranted, since we find, and it has been shown in autopsy

studies, that mural thrombi may be present by the third day after an acute myocardial infarction (see section on Mural Thrombus). Waiting two days before initiating anticoagulants means that the best one may hope for is to establish therapeutic prothrombin levels by the fourth day.

Burton [36] divided his patients into good- and poor-risk categories in retrospect and determined the incidence of thromboembolic complications and mortality in the two groups when they were and were not treated with anticoagulants. As may be seen in Table 21, although there was a reduction in the over-all figures for mortality and thromboembolic complications when comparing the good-risk group with the poor-risk group, there remains a similar proportion between the group receiving anticoagulants and the group not receiving them. There were both twice as many mortalities and twice as many thromboembolic complications in the control group as compared with the group receiving anticoagulants in both the good- and the poor-risk categories.

TABLE 21.—*Good-Risk Patients, After Burton* [36]

	Good Risk		Poor Risk	
	Anticoag.	Control	Anticoag.	Control
Patients, No.	98	58	163	184
Mortality	2(2%)	3(5%)	32(19%)	74(40%)
Thromboembolic complications	6(6%)	7(11.5%)	24(15%)	44(24%)

When one attempts to classify a patient according to Russek's criteria it becomes evident that several of these criteria are very vague. We agree with de Francisco [37] that it is difficult to interpret "significant enlargement of the heart," "other conditions predisposing to thrombosis," and "intractable pain." To attempt a clinical evaluation of heart size is well known to be fraught with error. To evaluate "intractable pain" is extremely uncertain and nebulous. Pain varies so greatly with the stoicism of the patient and the awareness of the house staff that it becomes almost totally unreliable. Also, just what is intractable pain? Is this only pain that cannot be relieved by frequent and high doses of morphine? Or is it prolonged pain requiring narcotics for several days but easily relieved by the narcotics? We certainly do not know the answers to these questions and therefore are hesitant to use pain as a prognostic sign. The only criteria which could be used with any degree of accuracy in this study were congestive failure, previous myocardial infarction, arrhythmias, and shock. Gallop rhythm and diabetic acidosis were either described or were present so infrequently as to be useless for this study.

The present series included 188 patients, or 30.6% of the total series, who, in retrospect, could be considered to have been good-risk patients. Of this number, 59, or 31.4%, received anticoagulation therapy. Eighty-seven, or 21.1%, of the poor-risk patients received anticoagulants. The mortality of the good-risk patients receiving anticoagulants was 3.4%, while the good-risk patients not receiving anticoagulants had a mortality of 20.9%. The patients receiving anticoagulation therapy in the poor-risk group had a 26.4% mortality, while the patients of the poor-risk group who were not treated had a 56.3% mortality. It may be seen from this that using anticoagulants in a poor-risk patient will increase his chances of survival to a level comparable to the good-risk patient not receiving anticoagulants. Also, giving anticoagulants to the good-risk patient increases the survival rate sixfold.

In considering the thromboembolic complications in the same manner, two patients receiving anticoagulants in the good-risk group had thromboembolic complications, for a 3.4% incidence. Good-risk patients who did not receive anticoagulants had a 8.5% incidence of thromboembolic complications. Poor-risk patients who received anticoagulants had a 6.9% incidence of thromboembolic complications, while the poor-risk patients without anticoagulation had a 17.5% incidence of thromboembolic complications. In both the good-risk and the poor-risk patients there were twice as

TABLE 22.—*Good Risk vs. Poor Risk*

	Good Risk		Poor Risk	
	Anticoag.	Control	Anticoag.	Control
Patients, No.	59	120	87	348
Mortality	2(3.4%)	27(20.9%)	23(26.4%)	196(56.3%)
Thromboembolic complications	2(3.4%)	11(8.5%)	6(6.9%)	61(17.5%)

many thromboembolic complications in the control group as in the group receiving anticoagulants. In fact, there were fewer instances of thromboembolic complications in the poor-risk group receiving anticoagulants than in the good-risk group not receiving anticoagulants. These data would support the thesis of Wright and his group who advocate anticoagulants in all patients with acute myocardial infarction (Table 22).

Conclusions

This thesis was prepared in an attempt to answer these questions:

1. What may be expected in the way of decreasing morbidity and mortality by the use of anticoagulation therapy?

2. Should anticoagulation therapy be applied universally or only in poor-risk patients?

3. How soon after an acute myocardial infarction should anticoagulation therapy be initiated?

This series included 623 patients with acute myocardial infarction as seen at The Ohio State University Hospital during the 16-year period from 1942 through 1957. There were 146 patients receiving adequate anticoagulation therapy, 369 patients not receiving therapy, and 108 patients who received anticoagulants but did not fulfill the criteria established for adequate anticoagulation therapy. A total of 248 patients (39%) died, and autopsies were obtained on 147 patients (59%).

In order to establish the validity of anticoagulants in this study, several of the ancillary methods of therapy, namely, bed rest, oxygen, narcotics, and sedation, were compared before and after 1950 to detect any major changes that may have occurred. There was a close agreement in all of these categories during the two periods studied.

The mortality in the group receiving anticoagulants was 17.1%. The group receiving inadequate anticoagulation had a 20.4% mortality, and the control group had a 54.5% mortality. The total incidence of thromboembolic complications was 5.5% in the group receiving anticoagulants, 17.6% in the group receiving inadequate anticoagulation, and 19.5% in the control group. The incidence of deaths attributable to thromboembolic complications was 1.4% in the group receiving anticoagulation, 3.8% in the group receiving inadequate anticoagulation, and 4.9% in the control group.

Strangely enough, the group receiving inadequate anticoagulation had almost an identical mortality to the group receiving adequate therapy, which would suggest that it does not matter whether a patient receives adequate or inadequate anticoagulation when considering mortality incidence. However, when one considers thromboembolic complications just the opposite would be true. That is, there is no appreciable difference between the patients not receiving anticoagulants and the patients receiving inadequate anticoagulants in the incidence of thromboembolic complications, but there is a marked difference between these two groups and the patients receiving adequate anticoagulants. The obvious discrepancy between the relation of mortality and thromboembolic complications in the patients receiving inadequate therapy can not be readily explained.

Complications due to anticoagulants occurred in 5.4% of the patients receiving adequate anticoagulation therapy and was responsible for 1.4% of the deaths in the group receiving anticoagulants. There was a 13.3% incidence of hemopericardium in the group receiving anticoagulants and a 4.8% combined incidence of cardiorrhexis-hemopericardium in the control group. Two patients of the group given anticoagulants were thought to have extended their myocardial infarction with subintimal hemorrhage.

We divided our patients according to Russek's criteria for the good-risk patient and had 188 patients, or 30.6%, who fit into this category. The good-risk patients not receiving anticoagulation therapy had a 20.9% mortality, but this was decreased to 3.4% when these patients received anticoagulants. There was a 56.3% mortality in the poor-risk group when no anticoagulants were used, and this could be decreased to 26.4% by anticoagulation therapy. The good-risk patients not receiving anticoagulants had an 8.5% incidence of thromboembolic complications, whereas the good-risk patients receiving therapy had a 3.4% incidence of thromboembolic complications. The poor-risk group not receiving anticoagulants had a 17.5% total incidence of thromboembolic complications, and this could be decreased to a 6.9% incidence by anticoagulation therapy.

We have demonstrated that one-sixth of the mural thrombi occur within three days after the onset of an acute myocardial infarction and that one-third have been formed by the end of the first week. Therefore, anticoagulation therapy should be initiated as quickly as possible to prevent these early thrombi from forming.

This study has shown that three times as many of the patients not receiving anticoagulation therapy died as in the group receiving therapy. There were also three times as many thromboembolic complications in the group not receiving anticoagulants as in the group receiving anticoagulants. Even though the mortality and morbidity in the good-risk patients are much less than in the poor-risk group, the good-risk patients receiving anticoagulation therapy had only one-sixth of the mortality and one-half of the morbidity of the good-risk patients not receiving therapy. We have shown that there is danger associated with the use of anticoagulants, but this is negligible compared to the preventable mortality and morbidity. Hence, we feel that all patients with acute myocardial infarctions should receive anticoagulation therapy and that anticoagulants should be started immediately.

Summary

A review of cases of acute myocardial infarction as seen at The Ohio State University Hospital over a 16-year period and the results of anticoagulation therapy on the morbidity and mortality are presented. The conclusions reached are that patients not receiving anticoagulation therapy have three times the morbidity and mortality of a comparable group of patients receiving therapy, that anticoagulants are effective and should be used in both good-risk and poor-risk patients, and that anticoagulants should be started as soon as possible after the onset of the acute myocardial infarction.

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Some Studies of the Comparative Biology of Human and Bovine Erythropoietic Porphyria

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Until recent years, the forms of porphyria were classified on clinical grounds alone. The photocutaneous symptoms common to Günther's congenital and chronic forms [1] have often led to confusion. Studies in this laboratory have revealed that the true porphyria congenita of Günther is an erythropoietic disease in which the site of abnormal porphyrin formation is the developing normoblast.[2-4] In contradistinction, the chronic, or "cutanea tarda," variety belongs in the category of hepatic porphyria, the fundamental disturbance being that of a great overproduction of porphyrin by the liver.[2,3] Human erythropoietic porphyria is a rare disease; in our own roster only 7 cases are represented in a total of 255, the remainder belonging to one of the hepatic categories, either intermittent acute, cutanea tarda, or combined types. Schmid and coworkers [4] found only 34 bona fide cases in the world's literature up to 1955 but pointed out that many cases of "cutanea tarda" type had undoubtedly been confused with porphyria congenita (erythropoietica). Thus, of the 86 cases gathered by Turner and Obermayer, in 1938,[5] only 18 were acceptable as porphyria erythropoietica.

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The inborn error in erythropoietic porphyria is the greatly excessive porphyrin formation in the nuclei of some of the developing normoblasts; these exhibit striking fluorescence in ultraviolet light and often contain benzidine-positive inclusions [4]; other normoblasts in the same cases appear entirely normal.

A bovine form of porphyria congenita is well known.[6-8] The available evidence, largely provided by Rimington and coworkers,[8,9] indicate that it is of erythropoietic type. However, the published data are incomplete with respect to the relative amounts of free porphyrin in the circulating erythrocytes and plasma and in the bone marrow and liver. Rimington and co-workers state that porphobilinogen was not demonstrable in the urine or in a liver biopsy specimen in bovine porphyria, "confirming that the disturbance of porphyrin metabolism was of the haemopoietic type." It must be emphasized, however, that in the pure cutanea tarda cases of the hepatic group porphobilinogen is likewise not demonstrable in urine or liver. Our observations in human porphyria have emphasized that the erythrocyte and plasma porphyrin values alone readily permit distinction of erythropoietic and hepatic forms. In bovine porphyria, the data differ in certain important respects but are nevertheless typically erythropoietic in pattern, and this is fully substantiated by the studies of porphyrin content of the bone marrow (normoblasts), liver, and spleen (see below).

The acquisition of a small herd of registered Holstein cattle, for metabolic studies,

would impose some peculiar clinical responsibilities on a department of medicine; fortunately, these are assumed by the veterinary members among us.* Many of the essential hematologic and genetic studies have been carried out by them; the porphyrin studies, in the Department of Medicine.

Certain advantages and disadvantages are at once apparent in a study of bovine versus human porphyria. When one is accustomed to the limitations of a few milligrams of human liver or bone marrow biopsy specimen, the prompt provision of a 50 gm. biopsy specimen of liver or a few inches of rib is peculiarly gratifying. The advantage of blood removal in amounts of 1-2 liters for chemical studies is at once evident. It must be equally obvious that the collection of 24-hour samples of urine and feces is much more difficult than in the human being. Our bovine metabolic ward has only just commenced its planned operations, and it will readily be understood that most of our data for the excreta, thus far, relate to concentration rather than 24-hour values. The collection of a 24-hour urine sample requires 24-hour vigilance of three capable attendants on 8-hour shifts. The volume of urine is in the neighborhood of 15-20 liters; the weight of the 24-hour feces is of the order of 10 kg.; as will be apparent, the output of porphyrin is staggering.

Of the seven cases of human erythropoietic porphyria in our roster, the last case, No. 246, has received the most extensive study with modern methods of any case thus far observed. This patient,† a woman 25 years old was seen at age 2 by Dr. Harriet Guild of The Johns Hopkins Hospital, at which time red urine, photosensitivity, splenomegaly, and anemia were already apparent. Prior to recognition of the light sensitivity, there had been repeated convulsions on exposure to sun; in addition, a marked photocutaneous ulceration had occurred. Chemical studies made at that time were reported by Dobriner et al.[10]

At present, this highly intelligent, cooperative young woman presents a striking appearance of long-standing photocutaneous disease. Because of splenomegaly and chronic hemolytic anemia requiring repeated blood transfusions, splenectomy was carried out by Dr. R. L. Varco, at the University of Minnesota Hospitals, on Dec. 13, 1957. The patient had been admitted on Nov. 26, the interval being employed for study of her porphyrin metabolism and for preoperative preparation. She recovered uneventfully and was discharged on Jan. 8, 1958. According to recent report, she has progressed favorably, without renewal of photosensitive manifestations (May 1, 1958). Various additional observations in this case will be described.

At present, 14 Holstein cattle are available for study: 7 homozygotes with manifest disease and 7 heterozygotes without manifestations. Three of the homozygotes, Nos. 1589, 1723, and 1726, have been examined in some detail, and of these No. 1584, familiarly known and henceforth referred to as Elsie,‡ has been investigated most extensively, both before and after splenectomy. In the interest of brevity, principal attention will be given to a comparison of the findings in Elsie with those in the human Case 246, just referred to.

The most reliable information on genetic aspects of the human form indicate that it is a non-sex-linked recessive trait, which is very compatible with the fact that, as yet, no families have been reported with cases in more than one generation.[4] The record of reproduction is almost nil. In the case of Kench et al.,[11] two infants were born to a porphyric mother; neither exhibited evidence of the disease. Case 71 has a younger sister with red urine and photosensitivity, but there was no history of additional cases in their family. Careful

* See footnote on first page.

† Dr. J. A. Hightower, Brunswick, Ga., referred this patient and provided information both before and after splenectomy.

‡ This case of bovine porphyria was originally observed by Drs. Harvey H. Hoyt and Victor Perman, College of Veterinary Medicine, University of Minnesota.

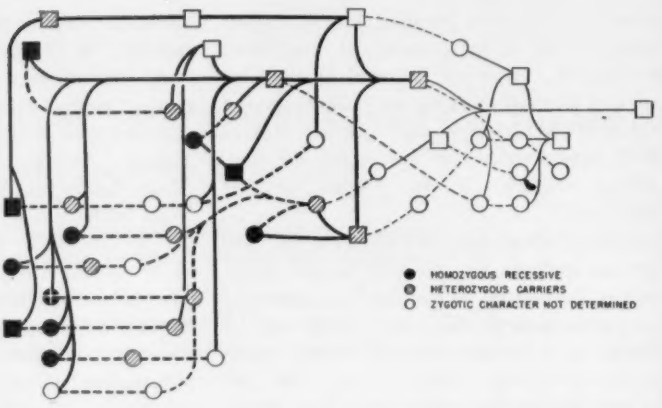

Fig. 1.—Genealogy of bovine erythropoietic porphyria. Elsie is represented by the black circle with white cross in the left lower area. The time from the first to last generation is approximately 30 years.

questioning has failed to reveal consanguinity in the parents or grandparents of either Case 71 or Case 246. The bovine disease is clearly a recessive trait,[6,7] as typified in Elsie's genealogy (Fig. 1).

In human erythropoietic porphyria, any area of skin exposed to sunlight is liable to photodynamic insult with vesicle formation and its sequelae. In Case 246, the scalp was severely involved in early infancy, requiring extensive skin grafting. These areas have all become richly impregnated with porphyrin during the subsequent 23 years, with the result that the entire scalp, now protected by a wig, exhibits intense red fluorescence in ultraviolet light. This patient's severest deformity is in her hands, which, at age 25, are peculiarly infantile due to mutilation and scarring in early childhood. In the black-and-white-Holstein porphyric animal, only the white areas are photosensitive, presumably due to filtering out of the exciting light by the black hair and increased skin pigment. This appears fully analogous to the situation of the sheep in some areas of the world, such as the Tarentine fields, where photodynamic compounds, such as fagopyrin and hypericin, together with natural selection have eliminated white sheep and left the black relatively unaffected.[12] It seems very likely that Negroes may have hepatic cutanea tarda, or perhaps even erythropoietic porphyria, without cutaneous manifestations. We have been privileged to study the excreta and liver biopsy specimen from a Negro man, observed by Galambos.[13] Here, the porphyrin data were typical of the hepatic "cutanea tarda" disease; yet this person had no cutaneous lesions. On the other hand, "cutanea tarda" porphyria is well known in the Bantu of South Africa.[14] It seems likely that photocutaneous manifestations depend on the degree of sun exposure, assuming similar concentrations of uroporphyrin in the blood and skin.

Comparison of the free porphyrins of the erythrocytes have revealed a striking and, as yet, unexplained difference between bovine and human forms. In the latter, uroporphyrin is preponderant by a wide margin; coproporphyrin, intermediate in amount, and protoporphyrin, but slightly increased above the normal range (20-65 mg/100 cc.). Typical data from the human Cases 76 and 246 are seen in Table 1, before and after splenectomy. Table 1 includes comparable data from three cows, Elsie being the only bovine porphyriac thus far splenectomized. In the bovine group, it is apparent that protoporphyrin was preponderant and uro- and coproporphyrin relatively small in amount. It is interesting, however, that at a later date, when Elsie had become pregnant, the erythrocyte uroporphyrin increased considerably and the protoporphyrin diminished; similar values are observed in bovine No. 1723, while in No. 1726 the data are like those recorded for Elsie when not pregnant. These

TABLE 1.—*Erythrocyte and Plasma Porphyrins in Erythropoietic Porphyria Before and After Splenectomy and in Hepatic Cutanea Tarda Cases*

	Date		Eryth. Porph., μg/100 Cc.			Plasma Porph., μg/100 Cc.		
			Uro-	Copro-	Proto-	Uro-	Copro-	Hb. Gm/100 Cc.
Erythropoietic								
Human	6/20/51	Before	440	150	105	5	26	10.1
Case 76	6/21/51	Splenect.						
	10/4/51	After	122	20	60	0	3.2	10.2
	11/27/51	Before	960	68	103	109	43.0	8.8
Case 246	12/13/57	Splenect.						
	12/31/57	After	109	110	192	19	21.0	13.5
Bovine								
	11/20/56	Before	16	3.4	1,080	27	12	4.8
Elsie	11/27/56	Splenect.						
	12/4/57	After	31	8.2	1,015	7	10	4.5
	4/7/58 *	After	76	11.0	515	6.5	11	8.3
No. 1,723	3/31/58 *		76	6.7	285	12.0	25.0	9.0
No. 1,726	3/27/58		6.1	2.9	515	1.0	4.2	11.7
Cutanea Tarda								
Human								
Case 191			0	0.5	29.0	16.5	2.4	
Case 152			0	0.3	27.0	5.4	0.8	

* Pregnant.

differences may well be related to the finding that the more fragile and presumably younger cells, selectively laked on an osmotic basis (Fig. 2), contain a much larger proportion, indeed, most of the uroporphyrin and a larger proportion of coproporphyrin, while the protoporphyrin appears to be rather equally distributed throughout the entire cell population. As yet, we have no comparable data for the human disease.

Table 1 also includes data from two human cases of hepatic cutanea tarda porphyria to show the contrast, mentioned at the outset, of the erythrocyte and serum (or plasma) porphyrin data with the values in the erythropoietic disease. In the former, the erythrocyte porphyrin content is normal, while the plasma porphyrins are significantly increased. In both human and bovine erythropoietic porphyria it is seen

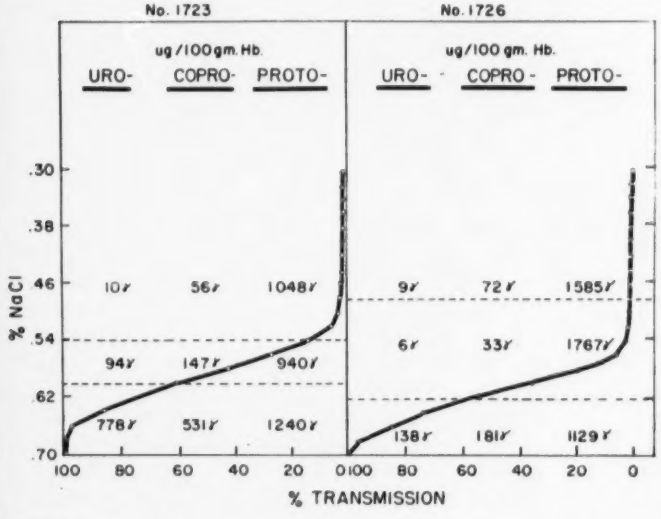

Fig. 2.—Fractional osmotic lysis of bovine erythrocytes (Elsie). Erythrocyte porphyrins in micrograms per 100 gm. of hemoglobin.

that the total amount of porphyrin in the red cells far exceeds that in the plasma; yet it is evident that in the bovine form the uro- and coproporphyrin content of the plasma may exceed that of the erythrocytes, unlike the relationship in the human disease.

The basis for the striking preponderance of protoporphyrin in the bovine porphyria erythrocytes is not clear and is receiving further study. The important question is whether this is, at least in part, an isomeric protoporphyrin of the Type I series corresponding with the great majority of the uro- and coproporphyrin of the bone marrow and excreta (see below) or whether it represents simply an excess of protoporphyrin of the ordinary isomer Type III series, unused in heme synthesis. The serum iron and tissue iron stores (bone marrow, spleen, and liver) are normal; hence, one would have to assume another cause than iron deficiency for an excess of this isomer. In respect to these questions, it is of interest to compare the bone marrow findings in the bovine versus the human forms of the disease as represented in Elsie and Case 246. The porphyrin data are given in Table 2. It is evident that there is

TABLE 2.—*Porphyrin Content of Bone Marrow in Porphyria Erythropoietica*

	Content, μg/100 Ml.		
	Uro-	Copro-	Proto-
Normal values approx.	1.0	5.0	100.0
Case 246	20,835 *	3,363	98
Elsie	8,000	829	500
Elsie	15,508 *	423	185

* Crys. m. p. 290-292 C (Type I).

rough agreement in the two species, with great preponderance of uroporphyrin consisting, in the main, of isomer Type I (ester m. p. 290-292 C).

It is seen in Table 2 that there is a distinct difference in ratio of the different porphyrins in Case 246 and Elsie. The first run on Elsie's bone marrow was on aspirated material; the second, on relatively dry marrow scooped out of a generous rib biopsy specimen and weighed. It is believed that the relatively greater amounts of copro- and protoporphyrin and the smaller amount of uroporphyrin in the first run may be due to dilution with circulating blood. Nevertheless, it is possible that the variations noted represent a change in rate of porphyrin biosynthesis, at least in part.

The bone marrow from Case 246 has provided the best photographs of unstained cells in the fluorescence microscope, showing again in striking fashion the much greater porphyrin fluorescence in the nuclei. While the fluorescence in the bovine marrow is generally less intense, the same pattern is evident; also, in stained preparations the same peculiar nuclear inclusions are seen as previously described for the human normoblasts.[4]

Splenectomy has now been carried out in seven human cases of erythropoietic porphyria: three of our own, including the presently described Case 246, and four reported by others.[15-18] Considerable variation in benefit has been noted, ranging from none to very great. The most beneficial result has been in our earlier case (Case 71),[3,19] in which the porphyria has remained entirely latent, without photosensitivity, since the splenectomy at age 4 years, the patient now being 13. The urinary porphyrin excretion at present is about one-third of what it was before splenectomy. Furthermore, there has been no recurrence of the hemolytic anemia, which constituted the chief indication for removal of the spleen.[19] In the second of our cases to be splenectomized,[3] little or no benefit was observed; this patient was not anemic, but had a mild increase in hemolytic activity. In two cases reported in the literature, significant benefit was conferred,[15,16] though in at least one of these it was of limited duration. In two cases, there was no benefit.[17,18] In the presently described Case 246 (see above), only five months have elapsed since splenectomy; as yet, the hemolytic anemia and leukopenia have not recurred, and there have been no new skin lesions, though it is undoubtedly true that there has been less sunlight exposure, incident to the winter

TABLE 3.—*Effect of Splenectomy on Urinary and Fecal Porphyrins in Porphyria Erythropoietica, Human Case 246*

	Urine, μg/Day			Feces, μg/Day		
Date	Uro-	Copro-	Date	Uro-	Copro-	Proto-
Normal	0.04	0.28		0.04	1.4	1.5
11/27/57	70.3	7.8				
11/30/57	112.8	18.7				
12/2/57	95.7	13.0	11/29-12/2	1.95	102.0	1.5
12/4/57	98.3	12.3				
12/13/57		Splenectomy				
12/14/57	19.0	7.4				
12/19/57	8.9	3.5				
12/26/57	8.6	4.6				
12/30/57	10.6	12.9				
			12/28-12/30	0.6	28.0	1.8
1/4/58	24.2	16.0				
1/8/58	35.0	22.7				
4/15/58	94.7	17.2	4/11-4/15	26.6	80.9	0.4

season and the enforced period of convalescence indoors. The essential data for the porphyrins are given in Tables 3, 4, and 5 for the excreta and tissues, respectively. It is evident that a rather marked decline occurred in the erythrocyte and serum porphyrins, as well as in those of the excreta. The urine became much lighter in the weeks after splenectomy; in fact, the patient stated that she had never before seen it have such a light color. It may be noted in Table 3 that for a time the porphyrin excretion diminished to about 10% of the presplenectomy values—very much in contrast to the data for Elsie, as shown in Table 4. Five months after operation, however, the level in Case 246 had returned almost to the preoperative values.

Insofar as the bovine disease is concerned, Elsie is thus far the only afflicted

TABLE 4.—*Effect of Splenectomy on Urinary and Fecal Porphyrins in Porphyria Erythropoietica in Bovine (Elsie)*

	Urine, μg/100 Cc.		Feces, μg/100 Gm.	
Date	Uro-	Copro-	Uro-	Copro-
11/20/56	2.93	.73	.14	4.92
11/27/56	3.45	2.04		
11/29/56		Splenectomy		
12/3/56	1.46	1.02		
1/8/57	3.8	1.64		
4/2/58	1.61	1.43	.065	6.1
Mg/day	212.8	188.8	10.4	972.0

member to be splenectomized. Benefit has been moderate. The anemia has been somewhat less marked; the reticulocyte percentage, essentially unchanged, and the plasma porphyrin concentration, moderately reduced. The urine and fecal porphyrins about two months after splenectomy and one and one-half years afterward were essentially unchanged. Representative data are shown in Table 4. The pattern of porphyrin excretion in the bovine disease is very similar to that in the human cases, with proportionately larger 24-hour amounts, uroporphyrin I being preponderant in the urine and coproporphyrin I in the feces.

Porphobilinogen has not been encountered in any of the human cases. A faint pink Ehrlich reaction has often been exhibited by the bovine porphyria urine, but the aldehyde compound has invariably been soluble in butyl alcohol, unlike that of porphobilinogen. The significance of the trace amounts of this Ehrlich reacting compound is not clear.

The porphyrin data obtained from the spleens and liver biopsy specimens are of considerable interest. These are contrasted

TABLE 5.—*Porphyrin Content of Spleen in Porphyria Erythropoietica*

	Content, μg/100 Gm.		
	Uro-	Copro-	Proto-
Human			
Case 246 (F 25)	5,259 *	474	63
Case 76 (F 7)	4,230	430	196
Bovine			
Elsie (F 2)	1,296 †	40	462

* Crys. m. p. 290-292 C (I).
† Mainly I (paper chromatography).

TABLE 6.—*Porphyrin Content of Liver in Porphyria Erythropoietica*

	Content, μg/100 Gm.		
	Uro-	Copro-	Proto-
Normal (human) values approx.	0	10	50
Human			
Case 246 (F 25)	18,140	1,647	365
Case 76 (F 7)	178	346	46
Bovine			
Elsie (F 2)	Trace	124	79

in Tables 5 and 6. It is seen that a remarkably large amount of uroporphyrin was present in the liver of Case 246, almost as much as in the bone marrow and considerably more than in the spleen. This was surprising, as in the two previous cases in which a similar comparison was possible [3] the amount of porphyrin in the liver was relatively very small, and this is likewise true of Elsie's liver, in which the values for copro- and protoporphyrin were not more than slightly increased and uroporphyrin was hardly demonstrable. Much of the porphyrin in the liver of Case 246 appeared to be in Kupffer cells, though our ability to correlate porphyrin fluorescence in unstained sections with ordinary histology of the liver is still too primitive to permit exact conclusions. At present, we are inclined to explain the large amount of hepatic porphyrin in this case, as contrasted with the small amounts in Elsie and our two previous cases in young girls, on the basis of age and consequent duration of excessive porphyrinemia. It is clear that the bones take up much of the excessive porphyrin which is not excreted, especially during early life when bone formation is most active. The ribs in Elsie, a 2-year-old heifer, were already deeply impregnated dark brown and intensely fluorescent; yet the liver contained but little porphyrin and essentially no uroporphyrin. Elsie's teeth are red-brown and fluoresce strongly in ultraviolet light. The presence of mild erythrodontia in Case 71 at age 4 years, with but little porphyrin in the liver, also supports a prior deposition in the bones. In Case 246, it is reasonable to assume that in the years after completion of skeletal growth the continued greatly excessive porphyrin formation in the normoblasts resulted in a more widespread, extraosseous porphyrin deposition, including the liver. This is reminiscent of the famous case Petry (age 40 at death), in which the studies of Borst and Königsdorffer [20] and H. Fischer and associates [21] revealed such extensive porphyrinization of the viscera as well as the bones.

The variable content of porphyrin in the spleen probably bears some relation to the rate of red cell destruction in the spleen up to the time of splenectomy. The greatest concentration thus far observed was in the youngest patient, Case 71, in whom there was a severe hemolytic anemia. In the presently reported case (Case 246), the hemolytic anemia was moderately severe and undoubtedly very chronic; here the splenic porphyrin concentration was considerably less than in the liver. It is conceivable that at least in this case, in which the total duration of the porphyria was very long, some of the hepatic porphyrin was derived from the destruction of porphyrin-laden erythrocytes in the spleen. The porphyrin concentration in Elsie's spleen is seen (Table 5) to have been about one-fifth of that in Case 246, and, as already noted, Elsie's liver contained only negligible amounts of porphyrin.

It is very clear, in any event, that the majority of the large amounts of porphyrin in the excreta, both in the human and bovine species, are not derived from porphyrin-laden erythrocytes destroyed in the spleen. A simple calculation in Case 246, based on circulating red cell mass, Cr^{51} life span (T $\frac{1}{2}$=15.5 d.) and red cell-porphyrin concentration, reveals that any fraction of the excreted porphyrin derived from destruction of circulating red cells would be very small indeed. Even if all of the circulating red cells in this case had been destroyed each 24 hours, the total amount of porphyrin which could thus be provided would have approximated 10 mg., a figure which may be contrasted with ca. 200 mg. total porphyrin excreted per day. The actual life span of the erythrocytes based on the Cr^{51} and fecal urobilinogen § data was probably between 20 and 30 days. The daily amount of porphyrin calculated similarly for a 20-day life span would be only 0.5-0.7 mg.

It appears highly likely that the principal source of excreted porphyrin in both species

§ 731 mg/d.; circulating red cell volume: 1,005 ml.; av. Hg 9/2 gm/100 ml.

is secretion by the developing red cells in the bone marrow. There is no evidence that these cells undergo destruction to release the large amounts of uro- and coproporphyrin excreted, and the appearance in the fluorescence microscope, as already mentioned, strongly points to a nuclear porphyrin formation, with release or secretion by intact cells.

Summary and Conclusions

Porphyria congenita of the bovine species is erythropoietic in type, fundamentally similar to human porphyria erythropoietica. The two diseases are readily distinguished by comparison of the values for the erythrocyte and plasma porphyrins.

The erythropoietic disease in both species is characterized by excessive formation of Type I uro- and coproporphyrin in some of the developing normoblasts. It appears that the formation is principally, if not wholly, in the nuclei and that the excessive porphyrin is released by intact cells, to be excreted in the urine and feces.

The erythrocyte porphyrin in the bovine disease is preponderantly protoporphyrin, while in the human form uroporphyrin is greatly in excess, the values for protoporphyrin being relatively normal.

The excessive porphyrin excretion in the human cases characteristically diminishes, at least transitorily, after splenectomy. In the single cow thus far splenectomized, no significant reduction was observed.

The liver porphyrin content was very small in the one cow thus far subjected to biopsy, similar to that observed in children with erythropoietic porphyria. In a 25-year-old woman having the disease since early infancy, the liver porphyrin content was markedly increased. This is considered to be due to the much longer duration of porphyrinemia, especially in the period beyond the active formation of bone.

Department of Medicine, University of Minnesota Hospital and Medical School (14). Irene Bossenmaier, Mary Weimer and Ruth Cardinal gave technical assistance.

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Case Reports

Acquired Agammaglobulinemia with Multiple Allergies and Pernicious Anemia

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A number of cases of agammaglobulinemia have been reported in the medical literature since Bruton [1] described the first case in 1952. This condition is encountered more frequently because patients who are unable to produce antibodies against infection are surviving now with the aid of antibiotics. It is recognized more readily because a high index of suspicion of this is becoming widespread, and methods of establishing the diagnosis by the study of serum proteins are now available to most physicians.

Two forms of isolated agammaglobulinemia exist: (1) a congenital type, occurring as a recessive sex-linked trait in male children, with symptoms developing in early life and serum γ-globulin levels reduced from the normal of approximately 1,000 mg. % to less than 10 mg. %, and (2) an acquired type occurring in either sex, with symptoms developing in adulthood and serum γ-globulin levels of 20-40 mg. %. Such a distinction may be arbitrary and more apparent than real, for those patients who develop the condition in adult life may have inherited a defect that is milder, not limited to the male sex, and late in making its appearance.

As Good [2] has pointed out, this disease is characterized by (1) increased susceptibility to infection, (2) absence of γ-globulin from the serum, (3) absence of antibodies from the blood and tissues, and (4) failure of antibody production in response to antigenic stimulation. A number of investigators [3,4] have demonstrated by the use of radioactive γ-globulin that there is no increased catabolism or loss from the circulation of this protein fraction in agammaglobulinemia. The primary defect apparently is a failure of the stem cell to differentiate to the plasma cell with a resultant deficiency in the production of γ-globulin and antibodies and an inability to respond to antigenic stimulation.

In addition to the isolated agammaglobulinemia, disturbances of γ-globulin synthesis may be found in persons having a marked hypergammaglobulinemia associated with decreased resistance to infection, in patients with multiple myeloma and excessive abnormal proteins closely related to γ-globulin, in patients with lymphosarcoma and lymphatic leukemia, and in children having generalized insufficiency of protein synthesis, including hypogammaglobulinemia.

Agammaglobulinemia should be suspected in anyone having repeated bacterial infections. A number of easily performed tests are useful to screen for this condition: 1. The globulin fraction precipitated by sodium sulfate in the standard chemical determination of the serum albumin and globulin is composed largely of β- and γ-globulins. Thus, in patients with a marked reduction of γ-globulins, i. e., agammaglobulinemia, the total "globulin" will be low and the A/G ratio increased. 2. Very low or absent isohemagglutinins in the serum of persons of Blood Group A, B, or

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O is indicative of the immunologic failure seen in these patients.[5] 3. Kunkel's zinc turbidity test shows 0 or traces instead of the usual five to six units. 4. Failure of antigenic response can often be suspected by the demonstration of a positive Schick test, since many people are Schick-negative as a result of childhood immunizations, or by the absence of agglutinins following a recent immunization.

It has been suggested that abnormally low sedimentation rates in spite of active infection,[6,7] and, in certain cases, unexplained splenomegaly and lymphadenopathy [8] should alert one to this possibility. Bone marrow and lymph node biopsy will show a significant reduction or absence of plasma cells. The diagnosis can be substantiated by serum electrophoresis.

We have recently had the opportunity to study a patient with agammaglobulinemia who also has pernicious anemia, hay fever, and asthma, with immediate skin reaction to a number of different allergens, as well as a delayed reaction to tuberculin.

Report of Case

A 42-year-old married, white male farmer was first admitted to this hospital on Nov. 4, 1955. He was well until the age of 28, when he began having a series of illnesses in February, 1943, shortly after entering military service. The first of these was epidemic parotitis, a disease which he had in childhood, followed closely by acute suppurative left posterior auricular lymphadenitis caused by a viridans Streptococcus, which responded slowly to oral sulfathiazole therapy, incision, and drainage. The erythrocyte count at that time was 4,260,000 and the hemoglobin 95%.

During the next six months he had meningococcic meningitis, acute appendicitis, wound infection with prolonged healing following appendectomy, and migratory pneumonitis. In August, 1943, he developed severe bronchial asthma and, in November, 1943, a bronchogram demonstrated bronchiectasis involving the right lower lobe. He was discharged from the Army in January, 1944, because of bronchiectasis and asthma. At that time his erythrocyte count was 4,700,000 and the hemoglobin 90%. From 1944 until his admission here in November, 1955, he continued to have a chronic productive cough and frequent episodes of fever and purulent sputum requiring antibacterial therapy. He was hospitalized on four occasions. Asthma persisted and hay fever appeared in 1946. Each seemed to be precipitated by ragweed, tree pollens, and dust, even in small concentrations. He lost weight and strength and was short of breath on slight exertion. In 1948, he was noted to have a hemoglobin of 10 gm. and a hematocrit of 35% and was given four transfusions. In 1950, he was hospitalized because of cough, fever, shortness of breath, marked weakness, lack of appetite, sore tongue, and paresthesias of his lower extremities. Ankle edema, jaundice, pallor, smooth red tongue, decreased vibratory sensation, splenomegaly, and diffuse lymphadenopathy were noted. Peripheral blood study revealed an erythrocyte count of 1,930,000, hemoglobin of 8 gm. %, hematocrit of 24%, platelet count of 52,640 per cubic millimeter, and reticulocyte count of 2%. Morphologic examination of the peripheral smear showed macrocytosis, leukopenia with relative lymphocytosis, and hypersegmentation of polymorphonuclear cells. Chemical determination of the total protein was 4.8 gm. %, with albumin 3.4 gm. % and globulin 1.4 gm. %. Gastric analysis revealed no free acid after histamine injection, and sternal marrow smears were described as "hypercellular, with marked megaloblastic hyperplasia and abnormal metamyelocytes typical of pernicious anemia." The diagnosis of pernicious anemia was unequivocally established. A reticulocyte response of 26% was obtained with parenteral cyanocobalamin (vitamin B_{12}) therapy. All hematologic findings returned to normal and have remained so on maintenance cyanocobalamin treatment. Figure 1 shows bone marrow examination in 1950 before treatment exhibiting megaloblastic red cell series. Figure 2 shows bone marrow examination in 1955, while on maintenance cyanocobalamin treatment. Note the absence of plasma cells. None were found after careful study.

After discharge, he continued having pulmonary difficulties as severe as before, and he was again hospitalized in January, 1954. Routine laboratory studies were normal, and sputum cultures revealed a variable pyogenic flora without fungi or acid-fast bacilli. Tuberculin test with 0.005 mg. purified protein derivative (second-strength PPD) was positive. He was considered unsuitable for pneumonectomy because a bronchogram showed extension of bronchiectasis from the right lower lobe to the right upper and left lower lobes, and he was discharged somewhat improved following treatment with antibiotics and postural drainage.

Respiratory infections persisted, and, because of continued asthma and hay fever, hyposensitization to dust, ragweed, and mixed fungi was tried from June, 1954, to July, 1955. Improvement was equivocal, so the injections were discontinued. Infection remained the dominant problem, and infiltration in the upper lobe of the right lung led to his hospitalization with a suspicion of tuberculosis in August, 1955.

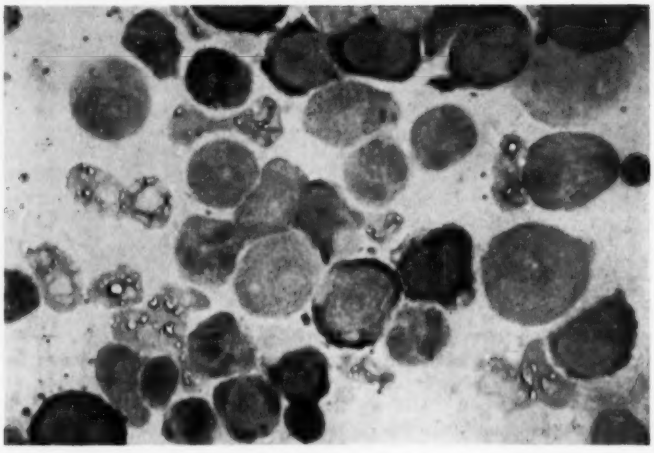

Fig. 1.—Bone marrow, 1950.

The previously described pulmonary findings were confirmed in an obviously chronically ill patient. The initial hemogram was normal except for a leukocyte count of 20,000 with a normal differential and erythrocyte sedimentation rate of 8 mm. per hour. Total serum protein was 6.2 gm. %, with albumin 4.7 gm. % and globulin 1.5 gm. %. Sputum cultures consistently yielded Haemophilus influenzae and Diplococcus pneumoniae. Typhoid and paratyphoid agglutinations were negative. Schick and PPD first-strength (0.00002 mg.) skin tests were positive, while those for blastomycosis, coccidioidomycosis, and histoplasmosis were negative. Paper electrophoresis of serum protein was reported as indicating agammaglobulinemia. Chest x-rays revealed bilateral scattered old and fresh infiltrations, and bronchograms demonstrated bronchiectasis of all lobes of the right lung. He improved on medical treatment and was transferred to this hospital.

The past history was unremarkable except as given. He had had a primary take to smallpox vaccination in childhood and a vaccinoid reaction in April, 1943. In addition to his respiratory allergies, he had bloating and diarrhea at times with ingestion of onions, cucumbers, apples, beans, and cabbage. The same foods precipitated paroxysms of asthma on rare occasions.

Family history, aside from the absence of similar illness in brothers and sisters, provided no relevant information.

Physical examination on admission revealed a normally developed, undernourished man, in no acute distress, with a frequent cough productive of copious purulent sputum. The exertion of being examined produced dyspnea. Temperature was 100 F; pulse, 96; respirations, 24; blood pressure, 110/76, and weight, 113 lb. Numerous rales and rhonchi were present throughout the left lower and

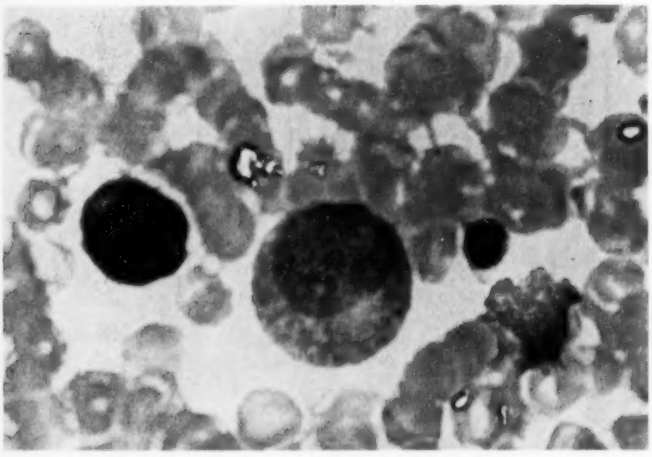

Fig. 2.—Bone marrow, 1955.

entire right lung fields; wheezing predominantly expiratory was noted over both lower lobe areas, and both the liver and spleen were palpable at the costal margin.

Laboratory studies indicated a normal red blood cell count, hemoglobin, hematocrit, reticulocyte count, platelet count, erythrocyte fragility, bleeding time, clotting time, clot retraction, prothrombin time, prothrombin consumption, urinalysis, and serum electrolytes. MCV was 86; MCH, 24, and MCHC, 28.8%. Blood group was AB, DcE. The white blood cell count was 14,000, with a normal differential. The erythrocyte sedimentation rate was 0 mm. in one hour. There was no sulfobromophthalein retention; alkaline phosphatase was 4.3; total serum bilirubin was 0.4 mg., with 0.05 direct and 0.35 indirect; serum cholesterol was 267 mg., with esters 60%; and cephalin flocculation was 3+ in 48 hours. Heterophile, cold, typhoid O and H, Salmonella, OX19, and Brucella agglutinations were negative. There was no cryoglobulin, and cardiolipin was nonreactive. Gastric analysis demonstrated no free HCl after histamine injections. Repeated sputum culture produced mixed flora normally occurring in the respiratory tract. Schick, Dick, and first-strength PPD (0.00002 mg.) skin tests were positive. The results of skin testing with various allergenic extracts and of passive transfer are noted in the table and show scattered sensitivities to foods and a reaction to room dust, with a positive transfer of this sensitivity. The results of the skin tests made in August, 1945, were obtained from his record. The skin tests recorded in 1955, 1956, and 1957 were done at this hospital. Treatment with immune globulin intramuscularly was begun in January, 1956. The Schilling test using Co^{60}-labeled cyanocobalamin showed an absence of the intrinsic factor, typical of pernicious anemia. Total serum protein (Biuret method) was 5.6 gm. %, with 4.6 gm. %, albumin and 1.0 gm. % globulin. Repeated determinations yielded similar results. Plasma fibrogen level was 225 mg. % and mucoproteins 265 mg. %. Gamma-globulin determined by the Kunkel method was 0.5 units. Moving boundary and paper serum electrophoresis showed no γ-globulin, with some increase in the α- and β-globulin fractions. Figure 3 shows a normal pattern on the left and that of the patient on the right exhibits an absence of the γ-peak. Figure 4 shows a series of paper electrophoretic patterns indicating only slight increase in γ-globulin while on treatment with intramuscular injections of immune globulin. A normal pattern is on the far right. X-ray of the chest showed the previously described lung disease.

The hospital course was characterized by a resolution of the low-grade fever, lessening of sputum volume, clearing of lungs, and weight gain of 7 lb. on treatment with postural drainage and parenteral penicillin.

He was readmitted in January, 1956, with symptoms related to increased activity of pul-

Serial Response to Skin Sensitivity Tests, 1945 to 1957 *

Allergenic Extract	Intradermal					Passive Transfer		
	Aug. 1945	Dec. 1955	March 1956	July 1956	Aug. 1957	Dec. 1955	March 1956	Aug. 1957
Dust (room)	1+	1+	2+	3+	3+	2+	2+	2+
Dust (barn)	0	0	0	0	2+	0	0	2+
Dust (hay)	0	0	0	0	—	0	0	—
Feathers	—	±	2+	2+	2+	—	—	—
Silk	—	±	2+	2+	1+	—	—	—
Wool	±	—	2+	3+	3+	—	—	—
Chocolate	1+	2+	2+	2+	2+	—	—	—
Bean, lima	—	—	3+	1+	1+	—	—	—
Beet	—	±	3+	3+	—	—	—	—
Celery	0	2+	2+	±	—	—	—	—
Potato (white)	—	—	2+	1+	1+	—	—	—
Potato (sweet)	0	—	3+	2+	2+	—	—	—
Apple	—	1+	3+	±	—	—	—	—
Banana	0	2+	3+	2+	1+	—	—	—
Pear	0	±	2+	±	—	—	—	—
Pepper (B & R)	—	±	2+	3+	1+	—	—	—
Trichophyton	1+	—	1+	1+	—	—	—	—
Penicillin	—	2+	1+	—	—	—	—	—
Pneumococcus	0	±	—	3+	1+	—	—	—
Influenza	0	—	—	1+	—	—	—	—
Trees	1+	±	±	±	1+	—	—	—
Grasses	—	±	—	—	—	—	—	—
Ragweed	—	—	—	—	—	—	—	—
Corn meal	—	—	2+	—	—	—	—	—

* Only allergens implicated by history or yielding positive results are recorded. 0 indicates not tested; —, no reaction.

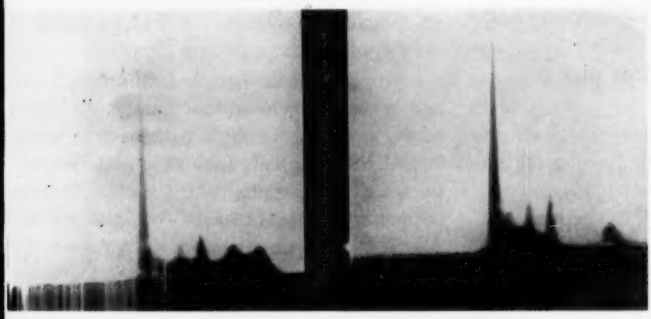

Fig. 3.—Electrophoretic pattern, 1955.

monary infection. A 14-day course of treatment with oral tetracycline and postural drainage again produced improvement in his chronic respiratory symptoms and a weight gain to 127 lb. Upon discharge, therapy with weekly intramuscular injections of 10 cc. of immune globulin was initiated. This amount is equivalent to approximately 0.1 gm. per kilogram of body weight per month and is the generally recommended maintenance dose; it has been continued to date.

The improvement at the time of his next admission in March, 1956, was striking. Cough was minimal, sputum was sparse and mucoid, and he could walk rapidly without shortness of breath. A routine hemogram was normal. Iliac bone marrow examination revealed no abnormalities aside from the complete absence of plasma cells. Skin and passive transfer tests were repeated with an apparent increase in the number and degree of skin reactions (Table). Serum protein was 5.2 gm. %, with albumin 4.3 gm. % and globulin 0.9 gm. %. In view of his clinical improvement he was discharged, and treatment with immune globulin was continued.

He was admitted for further observation in July, 1956, and in August, 1957. He maintained his increased exercise tolerance with continued immune globulin and cyclic oral tetracycline therapy but had paroxysms of asthma every few months requiring intravenous aminophylline and epinephrine for relief, particularly when exposed to dust at the time that he had a respiratory infection. In July, 1956, he was given a course of immunization with typhoid-paratyphoid vaccine and diphtheria toxoid and experienced a systemic reaction with fever and transient axillary adenitis after the first injection of typhoid vaccine.

Physical examination on these admissions showed transient rales in the base of the right lung, neither spleen nor liver palpable, and marked improvement. Laboratory studies were as before. Agglutinations to typhoid remained negative in spite of repeated vaccinations. The Schick test was negative in August, 1956, but was positive again in August, 1957. The first strength PPD (0.00002 mg.) remained positive. Repeated skin sensitivity tests were essentially unchanged (Table). The protein pattern seen on paper electrophoresis was unchanged (Fig. 4).

Comment

This patient is classified as a case of acquired agammaglobulinemia because of the apparent onset of the syndrome in 1943 at the age of 28 years with a history of

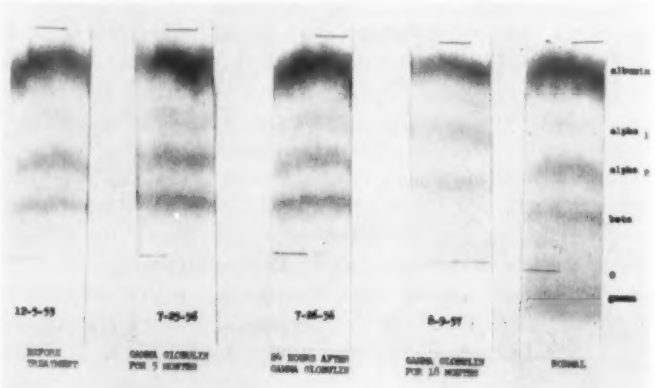

Fig. 4.—Serial paper electrophoretic patterns, 1955 to 1957.

prior excellent health. His serum γ-globulin level of 28 mg. % as determined immunochemically is lower than that of most previously reported adults.

Hematopoietic Abnormalities.—Since the basic defect in agammaglobulinemia may be due to an abnormality of reticular cell (multipotent mesenchymal cell) function, then a failure of development of the reticulum toward mature neutrophils, mature lymphocytes, or erythrocytes may be expected in some patients. Actually, many varieties of hematologic aberrations coexistant with agammaglobulinemia of both types have been described. These include lymphopenia,[9-12] eosinopenia,[13] neutropenia (cyclic,[13-15] transient,[13] and persistent [13,16,17]), hypersplenism,[6,13,17-19] "malignant lymphoma," [20] chronic lymphatic leukemia,[8] hemolytic anemia,[14,21] a picture resembling infectious mononucleosis,[8,17] extreme leukocytosis with infection,[13] thymoma,[13] and granulomatous disease [6] of indefinite specific type.

This patient's white cell response was normal, ranging from 8,800 when free of infection to 20,000 during a pulmonary infection. His most marked neutrophil response was 71%, and on one occasion when the total white cell count was 12,400 he had 53% lymphocytes with large abnormal cells reported on the smear.

Only two cases of agammaglobulinemia and pernicious anemia have been reported previously.[22,23] One of these also had diabetes mellitus. Our diagnosis of pernicious anemia is based on the typical clinical picture, achlorhydria, macrocytic anemia that responded hematologically to parenteral cyanocobalamin administration, and demonstration of the absence of intrinsic factor using Co^{60}-labeled cyanocobalamin (Schilling test) which indicates that the defect was not due to cyanocobalamin alteration but to the lack of intrinsic factor. Despite the fact that the anemia apparently developed after the onset of the dysproteinemia, since normal blood values were recorded as late as December, 1943, any relationship existing between these two conditions is only speculative.

The relationship between cyanocobalamin and serum protein is well known, for 99% of the cyanocobalamin is present in protein-bound form, probably with the α- or β-globulins.[23] The γ-globulin fraction has never been implicated; however, our patient responded to cyanocobalamin administered parenterally, indicating that the deficiency of γ-globulin does not affect its utilization, and the abnormal Schilling test proved that the defect was not due to cyanocobalamin alteration but to the lack of intrinsic factor. The limitations of knowledge concerning the intrinsic factor prevent us from drawing conclusions about the possible interrelations between it, red cell maturation, and γ-globulin.

There is a difference of opinion regarding the erythrocyte sedimentation rate in agammaglobulinemia. It is interesting that repeated determinations in our case were uniformly very low even in the presence of infection. Young, Wolfson, and Cohn [11] state, "The E. S. R. is consistent with the state of health or illness because fibrinogen, the chief plasma protein determinant of the sedimentation rate, shows its usual increase in response to illness or injury." Good [2] also stated, "As in normal persons acute disease in the patient with agammaglobulinemia produced a rise in E. S. R." A number of others [6-8,25] have reported cases with a normal or low sedimentation rate in the face of acute illness. Repeated determinations were made in our case with several readings of 0, a number of less than 4 mm. per hour, and the highest reading of 9 mm. per hour at a time when his infection was relatively slight. The muco-proteins were considerably increased to 265 mg. % and the fibrinogen 225 mg. % when the E. S. R. was 0. At another time the fibrinogen was 325 mg. % when the E. S. R. was 2 mm. per hour. It is obvious from the varying reports in the literature that the E. S. R. is dependent upon many factors that are poorly understood.

Allergic Manifestations.—The findings of immediate type skin reaction to allergens and delayed type skin reaction to tuberculin is of interest. Totally unexplained is the apparent increase in skin sensitivity after a period of immune globulin therapy. The production of antibodies is a function of the lymphoid tissue and γ-globulins compose but cannot alter or produce antibodies once these are formed.[2,26] Thus, it may be that the persons from whom the globulin was obtained had circulating antibodies to the allergens used in testing, and reagins were transferred passively. Similar passive transfer of diphtheria antibodies could account for the negative Schick test in August, 1956, which reverted to positive in August, 1957. This patient had a γ-globulin level of 28 mg. % which may have carried sufficient specific antibodies to cause a positive tuberculin and immediate type skin reactions.

The presence of circulating antibodies was demonstrated by the positive reaction to dust after passive transfer, and this was not influenced by the treatment with immune globulin. Reagins may be present in fractions other than γ-globulin, being frequently located in α- or β-fractions,[27] or even in more than one fraction in multiple sensitivity,[28] and may vary in location from patient to patient or may transfer from γ-globulin to β-globulin in the same patient.[29]

Although from the above discussion it is obvious that a patient with agammaglobulinemia can show evidence of allergies, to the best of our knowledge there have been no cases previously reported that showed skin sensitivity to multiple allergens and a positive passive transfer indicating the presence of circulating antibodies. Our patient apparently suffers from asthma of mixed etiology, the basic factor probably being chronic infection with the inhalant allergens precipitating acute attacks.

Summary

A case of agammaglobulinemia with allergic disease and pernicious anemia is reported. The patient has been under our observation for 2 years and has been followed for 18 months since institution of therapy with immune globulin.

A discussion of relationships between these conditions is presented.

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Treatment in Internal Medicine

Treatment of Acute Renal Failure

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Within the last decade much progress has been made in the understanding of renal physiology and disease due to the introduction of electron microscopy, and percutaneous renal biopsy. However, the clinician is still faced with the fact that he is generally unable to cure renal disease, or to effectively stay its progression. One exception is present—acute renal failure.

Acute renal failure is a clinical syndrome which is characterized by oliguria-anuria and progressive azotemia with electrolyte imbalance. Diseases such as acute glomerulonephritis, pyelonephritis, or obstructive uropathies are excluded because the injury to the kidney in acute renal failure is confined chiefly to the tubular cells and the basement membrane. It is true that the aforementioned disease may produce acute renal insufficiency, but the term acute renal failure is reserved for those cases which result from acute tubular damage produced by either nephrotoxic agents or renal ischemia. Acute renal failure is synonymous with the terms acute tubular necrosis, acute toxic nephrosis, and probably the most familiar and popular one, lower nephron nephrosis.

In a previous communication by Murphy [1] the high mortality due to nephrotoxins, incompatible blood transfusions, and the crush syndrome was reported. Lucke [2] grouped these disorders together in order to show that the pathologic lesion was essentially the same in all of them. A degeneration, and often necrosis limited to the distal segments of the tubules with brown casts of some heme compounds in the lower nephron and collecting tubules, occurred in this entire group of cases. Thus, he coined the term "lower nephron nephrosis." Many observers do not agree with this terminology, believing that each case of acute renal failure provides its own individual pathologic entity, and that usually the entire nephron is involved, not just the lower nephron.

With the damaging of the tubular epithelium the mechanisms which are chiefly responsible for maintaining the constancy of the internal environment of the body are severely disrupted. The existence of the patient is, therefore, greatly threatened. However, the lesion is potentially a reversible one, because the kidney has the ability to restitute tubular cells. Clinical management is designed to support and sustain the patient through that critical period when there is virtually no tubular function, until that time when adequate functioning nephrons can be obtained.

Even with our constantly advancing knowledge and techniques, the mortality of acute renal failure remains high. The extent of the tubular lesion is of great importance in determining the survival of the patient, but an almost equally deciding factor is the body's response to the precipitating injury. In those patients who do survive the question arises as to whether recovery of renal function is complete.

It is the purpose of this paper to summarize our experience with acute renal fail-

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ure at Milwaukee County Hospital during the last 10 years and thereby outline what we believe to be correct principles in managing the anuric patient. Generalities of treatment regimen can only be stated, and these must be adapted, since each anuric patient is a distinct clinical problem. Of greatest importance in the application of these principles is the experience which can only be gained from the bedside observation of anuric patients.

Material

Eighty-one patients with acute renal failure have been selected for presentation. Excluded from this study are (1) those patients seen prior to 1947, because of differences in therapy employed at that time, (2) patients who died within the first 24 hours, because it is our opinion that these patients died primarily from the precipitating cause of the renal failure, and not from the renal lesion per se, and (3) all patients who had known preexisting renal disease or who were subsequently found to have renal disease. Not all 81 patients were seen initially at Milwaukee County Hospital. Many were transferred to the renal service from hospitals in the surrounding areas at various times, in the oliguric phase of the disease.

Most important in the treatment of the syndrome is its early recognition. Too often the diagnosis is made accidentally and when the patient has been oliguric for one or more days. By this time ill-conceived treatment may have been applied. The oliguria is frequently discovered when a urine specimen which had been ordered cannot be obtained or when a nurse notes that the patient is not passing urine. The physician must be aware that acute renal failure may come from a variety of causes. Any patient who has had a transfusion reaction, was in shock from any cause or ingested a foreign substance, is a potential candidate for cessation of renal function. To illustrate this our experience is demonstrated in Table 1 where the various etiologies of the 81 cases are tabulated.

The greatest number of cases, 21, or 26%, are the result of shock. The degree of shock, as estimated by the depth and duration of the hypotension, had little correlation with the severity of the renal feature. The deciding factor was that shock was present, whether it was surgical, traumatic, or hemorrhagic.

The second most important causative agent is the incompatible blood transfusion which accounted for 19, or 23.4% of the total number. It is interesting to note that in three patients the anuria was the result of diagnostic x-ray procedure. Renal shutdown resulted after an aortogram in two patients, and after the administration of Cholografin (contrast medium) to one patient.

TABLE 1.—*Causes of Anuria in Eighty-One Cases Seen at Milwaukee County Hospital*

Cause		Cases, No.	Dead, No.
Shock		21	15
Operative	9		
Trauma	3		
Pregnancy	2		
Peritonitis	2		
Bowel obstruction	1		
Pancreatitis	1		
Gastrointestinal hemorrhage	1		
Unknown causes	2		
Incompatible blood transfusion		19	12
Cleaning fluids		7	3
Abruptio placentae		5	2
Crush syndrome		4	4
Mercury		4	2
Bichloride	3		
Thiomerin	1		
Sulfonamide		4	4
Associated with pneumonia		3	2
X-ray procedure with iodine		3	2
Aortogram	2		
Cholografin	1		
Miscellaneous		11	7
Hepatorenal	1		
Post TUR	1		
Burns	1		
Calcium hydrosulfite	1		
Lysol	1		
Arsenic	1		
Unknown	5	—	—
		81	53

An analysis of the cases is presented in Table 2. It will be seen that the cases are fairly well disposed through the fourth, fifth, sixth, and seventh decades. This might be expected, since the factors which precipitate the syndrome are probably more frequently encountered in the older person, that is, over 30 years, than in the younger patient. Although males predominate in this series, this is not of special significance.

TABLE 2.—*Analysis of Cases of Anuria by Age, Sex, and Race*

Age Group	Cases, No.	Sex		Race	
		Male	Female	White	Negro
10-20	4	3	1	4	0
21-30	9	4	5	7	2
31-40	17	8	9	14	3
41-50	13	6	7	12	1
51-60	13	10	3	10	3
61-70	17	10	7	14	3
71-80	6	5	1	6	0
81 & over	2	1	1	2	0
	—	—	—	—	—
	81	47	34	69	12

Methods

The course of acute renal failure is divided into three stages: (1) the stage of tubular injury which is of short duration, probably less than an hour, (2) the stage of oliguria and anuria, which varies greatly in its length but averages from 8 to 10 days, and (3) the stage of tubular recovery.

We feel that the syndrome may be minimized, or even possibly prevented from developing, if vigorous treatment is promptly instituted when the diagnosis is suspected. Whenever hypotension occurs, whether it be mild or severe, treatment should be intensive. The body responds to a fall in blood pressure by a generalized vasoconstriction in which the kidney vessels participate. The reduction in renal blood flow may cause ischemic change in the renal tubular cells, thus producing the syndrome or possibly potentiate the changes already produced by a nephrotoxic agent. Therefore, the circulating blood volume should be maintained by blood, plasma, or plasma expanders. Pressor substances, such as norepinephrine (arterenol), are of value in this stage. Even though they act by causing vasoconstriction, thereby initially producing a further diminution in renal blood flow, this is very short lived, for as the blood pressure rises Moyer[8] has shown that renal dynamics improve. In addition, myocardial contractility is aided, which, by increasing cardiac output, improves the renal blood flow.

In a mismatched blood transfusion alkalinization of the urine, by the administration of sodium bicarbonate, either orally or parenterally, probably has little to offer since, as Castle[4] has pointed out, the liberation of heme pigment is probably not the cause of tubular damage. Intravascular agglutination of red blood cells occurring in arterioles supplying renal tubular cells will cause ischemia and thereby tubular damage. Alkali administration may actually do harm, for the damaged kidneys will have a sodium load which they are not capable of excreting.

When a toxic substance is ingested it should be eliminated from the body or rendered inactive by the use of the appropriate measure as quickly as possible. Information from Poison Control Centers, which are now established in most major medical centers, is of invaluable aid in accomplishing this end.

Having survived the initial stage of the disease, the patient enters the oliguric-anuric phase which is the most critical. Tubular function has virtually been destroyed, and the patient has no means of excreting the products of protein metabolism. Their accumulation will ultimately threaten his life. More than this, the patient becomes a problem in fluid balance. It is here that the most frequent therapeutic error is made, because the patient's small fluid requirements are not appreciated, and he is overhydrated. The anuric patient has no effective means of handling an excessive water load.

Usually 600 cc. of H_2O may be safely supplied daily. This figure is obtained by subtracting from the daily insensible loss the water of oxidation which results from catabolic process. To this may be added varying amounts of H_2O up to 400 cc. daily, depending upon the degree of variation of the patient from the basal state. Of course, an equal volume of water must be added to replace urine output, and when there is overt loss, which usually occurs chiefly from the gastrointestinal tract.

Of aid in checking the state of hydration is the weight of the patient, which can be accurately determined by the use of a bed scale. An anuric patient will lose weight, since it is impossible to supply an adequate caloric intake. If no daily weight loss occurs, then the weight is being maintained by the accumulation of excessive water. Water intake should be controlled to produce a weight loss of about ½ lb. daily.

The body's small supply of endogenous carbohydrate is rapidly exhausted. Carbohydrate must be supplied if protein catabolism is to be diminished and if oxidation of fat is to proceed without ketosis. A minimum of 100 gm. of carbohydrate daily will accomplish this. Because fluid intake is limited, hypotonic solutions are necessary to supply this amount. By using a 10% sugar solution, (glucose or fructose) to which is added 95% ethyl alcohol, (up to 100 cc. daily) we have been able to supply the necessary carbohydrate calories through a peripheral vein. We have not routinely used indwelling catheters in deep veins which would be necessary if extremely hypertonic solutions were used frequently.

Oral intake is routinely discontinued throughout the oliguric stage. All fluids and calories are supplied parenterally, for only in this way can an accurate measure be obtained.

Protein catabolism is thought to be further diminished by the administration of testosterone propionate in dosage of 25-50 mg. intramuscularly daily.

The use of an indwelling uretheral catheter is to be avoided because of the certainty of renal infection. The patient should void if at all possible. If the patient does not void every 24 hours, catheterization is done using very careful technique.

As the anuria continues and the azotemia increases the electrolyte change of first importance is the rise in the serum potassium, for it causes a disruption of the conductive system in the heart. The best treatment of potassium intoxication is its prevention. At no time during the oliguric-anuric phase should potassium-containing substances be given. Infections, accumulations of blood, and areas of necrotic tissue should be

treated vigorously, for these liberate potassium with cellular destruction. Insulin should be given with the carbohydrate, for in its presence potassium is transferred intracellularly when glucose is deposited in the liver as glycogen. Twenty to thirty units of regular insulin administered simultaneously with the carbohydrate has been found to be adequate. This offers only a temporary measure, however, since as the glycogen is metabolized potassium is returned to the extracellular fluid. Once potassium intoxication has developed the best treatment is dialysis.

The anuric patient usually has a decrease in the serum sodium which, in the absence of actual sodium loss, is due either to dilution of the extracellular fluid, or the intracellular shift of sodium. Only if there is actual sodium loss do we give parenteral sodium solutions. To do otherwise will usually not raise the sodium but will frequently precipitate pulmonary edema.

Dialysis and the Artificial Kidney

As part of an integrated plan for the treatment of renal failure the artificial kidney is a valuable instrument. It is not a substitute for good medical management, but it is an adjunct in therapy. It is means to gain additional time to allow the damaged kidneys to reconstruct themselves if possible, and to resume physiologic function.

Several types of artificial kidneys are available. In this series of patients the Kolff rotating drum type of kidney has been used. It has the highest urea clearance rate of the kidneys currently used. The disposable coil kidney, which has gained popularity in the last two years has a urea clearance rate which is almost equal to the rotating drum type, and will give a clinical performance which is quite comparable.[5] Although its initial cost is low, the maintenance is high. All types of kidneys require experienced and skilled personnel to operate them if they are to be safe and effective.

Dialysis should preferably be a planned procedure, rather than an emergency one. Because the clinical conditions of patients vary greatly with identical electrolyte panels, no absolute rules can be given for dialysis. Generally we feel that dialysis should be considered whenever one of the following factors is present: 1. Serum potassium is 7.0 mEq. per liter. 2. The N. P. N. is over 200 mg. %. 3. The serum bicarbonate is less than 12 mEq. per liter. We have dialyzed patients who did not meet these criteria because in our opinion their condition warranted it. Important factors in making the decision as to when to dialyze are: the evaluation of the patient's general appearance, the cardiorespiratory status and the irritability of the neuromuscular system.

The only two contraindications to dialysis are: active bleeding from any source, or prolonged hypotension just prior to dialysis.

Treatment during the stage of tubular recovery, the diuretic phase, consists in supplying electrolytes as dictated by the serum levels, and urinary excretion. Reabsorption by the tubular cells is faulty at this time, and therefore, sodium and potassium depletion may occur. Fluids are given to maintain a urinary volume of 2,500 to 3,000 cc. daily. As azotemia decreases and nausea lessens oral fluids are started. Small amounts of 20% lactose are used initially and then other fluids added. Protein foods are generally not added until the N. P. N. is below 100 mg. %, and then protein restriction is continued until the N. P. N. returns to normal. During this stage the patient is rehabilitated as rapidly as possible with special attention being given to the vigorous treatment of any renal infection.

Results and Discussion

As Merrill [6] has stated, the recovery rate in acute renal failure is almost impossible to evaluate because of the concomitant illness of injury. Furthermore, only the more serious cases are generally moved to a renal treatment center, with the less severe and better prognosis cases being treated at the hospital of origin. This definitely influences the statistics.

All 81 patients were treated according to the principles which have been outlined. Sixty-two patients were treated conservatively, and of these 44 expired; for a mortality of 70.9%. In 19 patients dialysis with the artificial kidney was deemed necessary. It is doubtful whether these patients would have survived without dialysis, however,

TABLE 3.—*Mortality by Treatment Method*

Type	Cases, No.	Recovered	Expired	Mortality, %
Conservative	62	18	44	70.9
Dialysis	19	10	9	47.4
	—	—	—	—
	81	28	53	65.4

they were not preterminal at the time of dialysis. Nine of these patients did die which gives a mortality rate of 47.4% of the dialyzed patients. The over-all mortality rate of the 81 patients was 65.4% (Table 3).

It is difficult to compare results in patients treated without dialysis and those treated with the artificial kidney, for patients will respond to dialysis who would otherwise recover without it. In other words, dialysis early in the course of oliguria-anuria may not really alter the outcome of the patient provided good management is employed. It is also not fair to the patient to offer the artificial kidney as an instrument of last resort and use it only in those patients who are preterminal. It is, therefore, important that the physician be allowed to observe the patient throughout as much of his course as possible, in order that the clinical signs of impending damage may be appreciated before the chemical changes appear in the blood. Patients should, therefore, be transferred to a center where an artificial kidney is available early in the course of their illness.

Primary causes of death in the 53 expired patients (postmortem rate 75.5%) are listed in Table 4. Pulmonary edema was the most frequent cause, accounting for death in 15 patients. The pulmonary edema was almost always sudden in onset and occurred in spite of careful attention to fluid restriction. It occurred in patients who had been digitalized. Even though treatment—sedation, use of alcohol in the oxygen humidifier, rotating tourniquets and phlebotomy—was promptly instituted, the patients responded poorly. A few did survive the pulmonary edema, but most succumbed. Pulmonary edema did not occur as the result of dialysis. The rotating kidney is not an ultrafiltration device, but the patient did not gain water because of the high osmotic concentration used in the dialyzing bath. We feel that pulmonary edema is the greatest threat to the patient in acute renal failure.

Deaths were directly attributed to the precipitating injury in twelve of the patients. In 11 patients no primary cause of death could be determined, but failure to recover was a combination of factors. Irreversible changes provoked by uremia were responsible for death in seven of the patients. In retrospect, early dialysis in these patients possibly may have been life-saving. Hypotension which lasted for more than 24 hours and which did not respond to the use of blood and plasma replacement, plus pressor substances, were felt to be responsible for the death of five patients. In three patients acute myocardial injury terminated life.

Age of the patient seems to have a definite bearing on survival. The mortality by age group is presented in Table 5. It is lowest in the 21- 30-year group, where the mortality rate is 11.1%. In those decades over the fifth, with the exception of the ninth where

TABLE 4.—*Causes of Death in Fifty-Three Patients*

Cause	Patients, No.
Pulmonary edema	15
Preexistent disease	12
Uremia	7
Prolonged hypotension	5
Acute cardiac disease	3
Undetermined	11
	—
	53

TABLE 5.—*Mortality by Age Group*

Age Group	Cases, No.	Recovered	Expired	Mortality, %
10-20	4	2	2	50.0
21-30	9	8	1	11.1
31-40	17	9	8	47.1
41-50	13	3	10	76.9
51-60	13	2	11	84.6
61-70	17	4	13	76.5
71-80	6	1	5	83.3
81 & over	2	1	1	50.0

TABLE 6.—*Analysis of Deaths in Fifty-Three of Eighty-One Patients Dying with Acute Tubular Necrosis—Length of Survival After Anuria*

Day of Anuria	Patients, No.
1	1
2	3
3	6
4	4
5	4
6	6
7	6
8	4
9	4
10	3
Over 10	12
	53

there are only two patients, the mortality rate is in excess of 75%. Advancing age would seem to influence the prognosis unfavorably. Acute renal failure is encountered more frequently in the older age groups because these people, as a group, are exposed to more extensive surgical procedure. The risk of complications is, therefore, greater and especially so if blood is used.

In Table 6 the length of survival after the onset of oliguria is presented. Death may occur at any time in the course of acute renal failure, but any one period does not seem to pose a greater risk to the patient. However, after the 10th day of anuria, even though dialysis is employed, the risk of death becomes very great even though the theoretical chance of survival improves because of tubular regeneration.

In Table 7 the length of survival after dialysis in nine fatal cases is shown. These

TABLE 7.—*Survival in Nine Fatal Cases of Anuria Who Were Dialyzed*

Anuric Day on Which Dialysis Done	Patients, No.	Survival After Dialysis, Days
4	1	3
5	1	1
8	2	1, 7
9	1	1
10	3	½, 1, 2
12	1	1

patients were not preterminal at the time of dialysis, but yet with three exceptions they did not survive longer than 24 hours after dialysis. In each case chemical correction of the blood was obtained, and dialysis was deemed satisfactory. Apparently, an irreversible change had taken place which was not corrected by dialysis.

Presently, data are being gathered on the recovery of tubular activity following acute renal failure and will be reserved for a further communication.

Summary

The prognosis of acute renal failure is poor and is dependent to a great degree upon the nature and severity of the precipitating injury or illness, as well as the extent of the renal lesion.

Shock was the cause of failure in 21 of the patients in this study, whether it was surgical, traumatic, or hemorrhagic. Incompatible blood transfusion was the second most important causative agent. Whatever the source, renal failure is more apt to occur in patients from 30 to 70 years of age.

The mortality may be reduced if the patient is closely managed by a regimen which (1) rigidly restricts fluid and electrolyte intake, (2) controls protein catabolism, (3) minimizes serum potassium rise, and (4) supports the cardiovascular system.

The oliguric-anuric phase is the most critical, and fluid balance presents a problem. Usually 600 cc. of H_2O may be safely supplied daily, depending upon the degree of variation of the patient from the basal state. An equal amount of water is then added to replace urine output, and when there is overt loss. Weight of the patient should be closely watched and determined daily by the use of a bed scale. By using a 10% sugar solution (glucose or fructose), to which is added 95% ethyl alcohol (up to 100 cc. daily), the basic carbohydrate calories can be supplied. All fluids and calories are given parenterally in order to obtain an accurate measure.

An indwelling catheter should be avoided if possible. However, in the event the patient does not void every 24 hours catheterization may be done, using very careful technique.

Potassium-containing substances should not be given any time during the oliguric-anuric stage. Twenty to thirty units of regular insulin may be administered simultaneously with the carbohydrate as a temporary measure to decrease the serum potassium.

Dialysis with the artificial kidney is a valuable therapeutic agent and has been responsible for decreasing the mortality. Indications for its use are discussed. The contraindications to dialysis are: active bleeding from any source, or prolonged hypotention just prior to dialysis.

The experience with acute renal failure in 81 selected patients at Milwaukee County Hospital has been reviewed. Sixty-two patients were treated conservatively; in nineteen patients dialysis was employed. Pulmonary edema was the most frequent cause of death.

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Syphilis

Review of the Recent Literature

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Many of the problems covered by the literature on syphilis during this review period (July 1, 1957-July 1, 1958) have been summarized by Fiumara [1] in a paper with the provocative title, "Sic Semper Syphilis." He notes that the tremendous improvements made since 1938 in the control of this disease have been due to the organization and operation of venereal disease control programs and to the effect of penicillin in decreasing the period of infectiousness. Problems involved are the sexual promiscuity of the population, failure of private physicians to report cases, inherent limitations of control methods, mobility of the population, and overoptimism in assuming that the disease has been beaten. Syphilis cannot be totally eradicated, but the incidence rate can be reduced by effective cooperation of an organized health program and alert private physicians. Both are required. Attention is called to the increase in allergic reactions to penicillin—also, to the possibility of developing an effective vaccine. Evaluation of therapy has received relatively less attention in this 23d annual review, but there is continued interest in one of the chief concerns of the 22d,[2] namely, the present problem of syphilis. There is expression of both optimism and pessimism as to the possibility of the eventual complete eradication of this disease.

King [3] voices an excellent plea for the strengthening of venereal disease control at a time when there is increasing lack of interest because of the decline in incidence. He feels that the reduction in venereal diseases since the second world war is probably due more to favorable social conditions than to the new antibiotics. Of all the venereal diseases, only syphilis appears to be much affected by campaigns for control, and even for syphilis the ultimate outcome remains in doubt. It seems that, although the venereal diseases are certainly not dying, there is a danger of the decline of venereology. The combination of thriving diseases and the disappearance of those whose special study they are has obvious dangers for the public health. It seems essential that the structure of the venereal disease service should be maintained. Too much of the venereal disease organization is being dismantled by those inspired with false confidence by the postwar decline in incidence and the several new drugs.

The first of a series of Buffalo General Hospital-University of Buffalo conferences on clinical bacteriology and immunology is entitled, "Who Has Syphilis?" [4] This is an interesting, stimulating, and thought-provoking presentation of the problem of syphilis as it is met today by the various specialists in clinical practice.

J. Earle Moore [5] editorializes that the 1956 trend in the incidence of syphilis is

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still downward. That which has appeared in the lay press and the "Joint Statement" that the "optimism of the past few years has proved disastrous" seems hardly justified by the cold, bare epidemiologic facts. Though there was an increase of 241 cases of definitely infectious (primary and secondary) syphilis reported by state health departments among the civilian population of the United States in 1956 over 1955, there was a decrease of 1,439 cases of potentially infectious (early latent) syphilis, and, therefore, a net decrease of 1,198 cases of actually or potentially infectious syphilis. In terms of case rates per 100,000 population, primary and secondary syphilis remained unchanged at 4.1 and these combined with early latent syphilis decreased from 17.5 to 16.4. Apparently, Moore did not take into account that (1) the decrease in early latent syphilis probably represents lessened incidence for the year before and not for the year under consideration; with increase in primary and secondary cases, it will probably follow that there will be an increase in early latent syphilis in a year or two; (2) with lessened emphasis on clinics and public health efforts, more cases are probably being treated by private physicians with a consequently smaller number of cases being reported.

According to Hermann,[6] prior to World War II Holland had few cases of the venereal diseases in spite of no special control measures. In 1926, a Center for V. D. Control (an "advice office" located one in each district throughout the country, serviced by a medical adviser and a social worker) was established, but there were no compulsory measures. Considerable increase in these diseases followed Holland's entrance into the war in 1940 (from 272 to 578 in 1941 and to a maximum of 1,436 in 1945). During the war Germany introduced a compulsory law similar to the German State Law for V. D. Control; this law was abolished by the Dutch after the war. Incidence leveled off to 135 cases among civilians and 324 among seamen in 1954. A sharp rise was noted among both groups in 1955 and a small decrease in both groups in 1956. Figures for 1956 are 128 cases among civilians and 379 among seamen. Hermann believes that these data emphasize the importance of a V. D. clinic in all large seaports, as well as the necessity for maintaining a nucleus of staff personnel trained in V. D. control methods, both from the medical and social standpoints.

Figures taken from the "Analysis of the Total Number of New Patients Attending the Clinics in England and Wales During the Quarter Ended 31st March, 1957" as reported in the Monthly Bulletin, Ministry of Health, Great Britain, August, 1957, show that in the first quarter of 1956 and 1957 the number of cases of syphilis were the same (1293 and 1292). In a report published in 1958,[7] dealing with the year 1956, the Chief Medical Officer states that the slight increase in the number of new cases of early infectious syphilis that occurred in 1955 has continued in females but not in males, and in 1956, 587 men and 257 women attended the clinics for the first time as against 609 men and 228 women in 1955. More new patients with late and latent stages of acquired syphilis also attended clinics in 1956 (3,707 as against 3,582 in 1955). It is hoped that the routine tests are disclosing a greater number of unsuspected infections, although it is recognized that some of these are immigrants with yaws rather than syphilis. Congenital syphilis has continued to decrease, and the infantile death rate from syphilis is reported as zero. The percentage of positive results in pregnant women has remained about constant from 1953 to 1956 (0.21% to 0.28% primipara and 0.43% to 0.35% multipara). In his annual report for 1956, Perkins,[8] Health Officer for Middlesex, England, also noted that the number of patients attending venereal disease clinics remained at about the same level as in 1955. He drew attention to the increasing number of girls under the age of 18 attending these clinics. Laird[9] reports that from 1948 to 1956 acquired syphilis of less than one year's duration declined in the highly industrialized and con-

gested seaport area of Manchester, England, from 977 to 11 cases per year. In smaller towns outside Manchester the decline was from 716 to 31 cases per year. Laird states that the marked decline in infectious syphilis has made it easier to trace the epidemiologic chains of infection. Previously, endemic syphilis had become sporadic, some cases leading to minor localized epidemics. In 1956, for the first time there was less infectious syphilis in Manchester than in the surrounding areas. Laird [10] also states that in 1956 over half of the early syphilis seen in the Manchester area was imported from outside the area and that prostitutes were responsible for one-third or more of the infections in men. Towpik [11] finds that the incidence of primary, secondary, and congenital syphilis in Poland has decreased by 98% from 1947 to 1955, whereas the gonorrhea rate has declined by only 39%. An epidemiologic analysis of cases of lues recens in Cieplice (Silesia) was made by Kolankowski.[12] The increase of fresh cases seems to be connected with the considerable increase of frequentation of the place, a well-known summer and health resort. The author stresses the importance of combating such sources of infection as prostitution and alcoholism and emphasizes the importance of sanitary education, of careful control of the public holiday homes, and of strict observance of the recommendations of the Health Ministry concerning the follow-up after treatment of gonorrhea cases as possible cases of syphilis. The causes of increased morbidity rate of syphilis in the Gdansk area of Poland in 1955-1956 are discussed by Miedzinski and Markiewicz-Szumska.[13] This increase could be effectively combatted by means of modernization of all the methods of syphilis control which proved satisfactory during the after-war years.

The incidence of postmortem syphilis among the South African Bantu was studied by Hill, Griffiths, and Buckle.[14] They used postmortem records of two Durban hospitals. Unfortunately, in many cases no histologic examination was made of the tissues of the central nervous system or aorta. The records included 1,030 Bantu and 534 Europeans. There was approximately 2.9% syphilis among the Bantu and 0.4% among the Europeans. These figures may be unduly weighted by the large number of subjects under 15 years of age. Disregarding this group, there is an incidence of 5.5% among the Bantu and 0.5% among the Europeans. Assuming that only 50% of syphilitics show postmortem evidence of the disease, the true incidence of syphilis becomes 11% among the Bantu and 1% among the Europeans.

The present status of syphilis in the United States is reflected in a number of papers. The American Social Hygiene Association [15] has reported that the total number of reported cases of syphilis in all stages has risen in the United States for the second consecutive year. During 1957, there were 135,542 cases of syphilis reported, as compared with 126,219 in 1956, and 122,075 in 1955. Thomas [16] outlines syphilis control in upstate New York, where reported cases of primary and secondary syphilis have been steadily increasing since 1953. The number of such cases reported in 1956 was more than double those reported in 1953 (134 compared to 65). Early latent syphilis of less than one year's duration (believed to be infectious) decreased from 1953 to 1956, when an increase above the number reported in 1953 occurred. Thomas concludes his article as follows:

1. Serologic tests for syphilis should be made when there is the slightest suspicion that syphilis might have been acquired. This rule applies especially to all persons infected with gonorrhea or who have a urethral discharge. 2. All syphilis cases should be reported promptly to local health departments. 3. Early cases of less than one year's duration should be interviewed for contacts, preferably by personnel from health departments. Local health departments will locate and refer contacts to the physician. 4. Following a diagnosis of syphilis, treatment should be initiated promptly, and it should be completed as soon as possible. In early and latent cases, a single treatment with 2,400,000 units of benzathine penicillin will usually suffice. 5. State and local health departments are prepared to render consultation and epidemiologic services to physicians who diagnose or treat syphilis. 6. The cost to taxpayers of hospitalizing advanced cases of neurosyphilis is still great in New York

State. This can be prevented by finding and treating asymptomatic cases of syphilis.

Parker,[17] of Nebraska, notes that the more intensive and intelligent epidemiological efforts plus penicillin therapy have decreased total incidence of syphilis but have not solved the venereal disease problem. The increase in venereal diseases among teen-agers, the persistent static rates in the incidence of gonorrhea, the slight rise in total number of syphilis cases, and a possible false sense of security among the population are all cause for concern. Cooperative educational efforts are needed among doctors, public schools, and health departments. Doane [18] describes the status of venereal disease control in Texas, where the situation proves to be the same as in other states. Too many physicians, including public health doctors, eagerly proclaimed that venereal diseases were solved problems. Budgets were slashed, personnel reduced, control programs curtailed. Today, reports show that the incidence of infectious syphilis is rising. Doane contends that there exists much more infectious syphilis which a carefully directed program could reveal. It is remarkable that wherever they intensified case-finding techniques in the state of Texas the morbidity of infectious syphilis rose. In those areas where a decline has been noted, one finds that very little is being done in active case finding. Although there was a downward trend in syphilis to 1956, DeOreo [19] reports that in 1956 there was a nationwide increase of 9,133 cases of syphilis reported; Ohio showed increase in both primary and secondary syphilis, and syphilis ranked third in number of cases reported in Cleveland (measles and gonorrhea was first and second). In view of the current reservoir of 2,000,000 in the United States, as estimated by the Public Health Service, urgent action is needed to diagnose and treat primary and secondary syphilis and follow-up contacts; however, the reservoir will be reached mainly through routine blood testing. This testing must be done in the office of the private practitioner, in hospitals, and in outpatient departments. Today most cases of venereal diseases are handled by general practitioners, who can do much for the community as well as the patients by active participation in a program to reduce the ravages caused by these "still too common plagues." The Virginia Venereal Disease Control Committee Report [20,21] initiates an effort to compare the venereal disease rate in 1956 and 1957. The syphilis reported morbidity rate per 100,000 population in 1955 dropped in 1956, but a considerable increase was shown in gonorrheal infections. For 1957, a 30% increase of verified lesion syphilis was experienced for the first six months. This increase is largely due to several small epidemics in three widely separated areas of the state. The Committee realizes that the methods of morbidity reporting were inadequate, since many physicians and hospitals fail to report venereal disease information as required by the state. For the fiscal year 1956-1957, there were 800 cases of reported early syphilis and 6,751 cases of reported gonorrhea in the state of Virginia.

Clarke,[22] writing in *Today's Health* for the nonmedical reader, describes in clear terms what has happened to the venereal disease control program in the United States. He feels that the principal factor in the decline of syphilis after World War II was not penicillin but the restoration of relatively normal social conditions that had been deeply disturbed by war. The vigorous execution of the case-finding, diagnostic, and treatment program, plus the restoration of normal peacetime social conditions, brought down the syphilis incidence rate in a spectacular dive from 1948 to 1956, when the trend was reversed. The drastic cut in funds for venereal disease control has resulted in fewer diagnostic and treatment facilities almost everywhere in the United States. This factor, plus inadequate case finding, has allowed the incidence of syphilis to increase even under the relatively normal peacetime conditions existing at present.

Morbidity reports by public health centers in various countries, which compare the incidence of syphilis of the period of 1952-1955 with the period 1943-1947, reveal a

decline of the disease of between 66% and 92% in recent years. The period 1943-1947 corresponds to a period of increase of venereal diseases due to the war. Touraine [23] believes that a more realistic assessment can be obtained by comparing the period 1952-1955 with the period 1930-1939, when social conditions were more stable. Such comparison would yield a decline of only 26%-80%. Another interpretation may be that the fall of reported cases of syphilis in recent years shows only a short down-swing of the secular cyclical trend of this pandemic. The results of serologic tests for syphilis reveal that the decline in number of patients with recent latent and congenital forms of the disease as shown in morbidity reports is smaller than those obtained through clinical evidence. There are indications that the incidence of primary and secondary syphilis has again risen in various countries after 1955, despite extensive syphilis control programs. Recrudescence of syphilis is due to various individual and general factors. The individual factors are negligence of the patients to seek treatment and occasionally poor cooperation by the physicians to support the venereal disease control programs. On a broader basis, prostitution and incidence of syphilis rise during the periods of economic prosperity, war, and population migrations. Foreign workers, jail inmates, and clandestine prostitutes are more exposed to the disease than other groups. Certain regions of the world are a sort of perpetual reservoir of the infectious agent. These reservoirs can be eradicated only through an effective world health program. King [24] discusses the papers related to venereology which were presented at the International Congress of Dermatology in Stockholm in 1957. The presentations covered serology of syphilis, epidemiology of the treponematoses, long-term results in the treatment of syphilis, and nongonococcal urethritis.

Literature

The literature on syphilis has been enriched during this review period by a number of compilations. Doepfmer [25] has reviewed the progression in syphilis. Wortmann's [26] comprehensive Annual Survey of Syphilis covers the same period as our 22d review (July 1, 1956 to June 30, 1957). Willcox [27] wrote the 1956, or 10th, of a series of annual reviews of the world's literature concerning venereology. In addition to the material surveyed in our annual review of syphilis, Willcox covers the contributions about the other venereal diseases, nongonococcal urethritis, and trichomoniasis. Needless to add, all of the articles cited are essentially annotated bibliographies and are no substitute for the reading of the original papers, which should be consulted as required. Hudson's [28] monograph on bejel, a disease name he gave to the outside world, which was the local word for a disease prevalent among Bedouin peasants, covers this subject from the historical, clinical, and serological standpoints. Hudson [29] in another presentation that can hardly be called historical, sets forth the hypothesis that the original treponematosis was similar to yaws and originated thousands of years ago in Africa as a disease of childhood propagated under the unhygienic conditions of primitive village life. Following migration to more temperate climates, endemic syphilis developed, and when people moved to cities venereal syphilis ensued. Hudson feels these three represent the reaction between man and the treponeme under three different environmental patterns. He considers they are evolutionary phases of one disease and should, therefore, all be termed treponematosis. Nicol [30] has written an interesting note of appreciation of Julius Wagner von Jauregg, the father of malarial therapy of neurosyphilis. The history of the inception and growing importance of dermatovenereology as a specialty is reviewed for Denmark by Haxthausen,[31] for Finland by Sonck,[32] for Norway by Danbolt,[33] and for Sweden by Thyresson.[34] The various important contributions of men from these countries are discussed.

Syphilis in Shakespeare's Tragedies.—Hahn [35] points out that even a casual study of the tragedies written by Shakespeare in

1601-1609 indicates a remarkable knowledge of medical and surgical subjects and the symptoms and progress of disease. Incidences are noted from "Hamlet," "King Lear," "Julius Caesar," "The Tempest," and "Macbeth." However, "Timon of Athens" is discussed at some length as representing an interestingly accurate clinical picture of progressive paretic dementia (undescribed as a clinical entity in Shakespeare's time). Additional passages are cited as descriptive of syphilitic symptoms, and the author suggests that for students of the history of syphilis, "Timon of Athens" is more than a less important Shakespearean play—rather a classic and source book in this connection.

Experimental Syphilis

The activity in the experimental syphilis field, as indicated by the literature of this review period, is still at a high pitch. This interest is not limited to serologic problems, which would have a wider application because of false reactions but covers many facets of the syphilis problem: culture of Treponema pallidum; immunity; mouse syphilis; allergy, antibiotic therapy; effects of cortisone; radioisotopes and rabbit syphilis, and intradermal reactions. There are, of course, other aspects of experimental syphilis which will be touched upon in the clinical section of this review. This range of studies, as well as their number, is in keeping with the coverage of the previous review.

From eight trials of an intradermal reaction with luetin prepared from a suspension of Nichols treponemes, Duverne and Mounier [36] have come to believe that the test may prove useful as a supplementary measure in diagnosing syphilis, particularly latent syphilis. They feel it may be used in surveys and to some extent may indicate the modes of treatment needed. Simeray,[37] employing the intradermal luetin test, made a brief report on results of 75 further tests. He has never found a reaction in a healthy person or one with primary syphilis; he wonders whether repeated use of luetin in cutaneous tests would not produce an allergy, i. e., a reactive result eventually. He showed a graph of the cutaneous reactions of patients treated for syphilis who had nonreactive serology but were TPI-reactive and states that these cases behaved from the point of view of cutaneous allergy in the same way as did untreated syphilis cases or treated cases in which the serologic tests were irreducibly reactive.

New Culture Method for Organisms of Leprosy, Tuberculosis, and Syphilis.— Gurun [38] discusses a new method for culture of three organisms, including virulent T. pallidum. He used the following elements in all three culture media with variations only in water content: Beeswax, 20 grains (1.3 gm.); neutral almond oil, 20 grains; sugar (sucrose), 20 grains; distilled or tap water, 20-40 cc., and egg yolks, 2. During experiments the basis of culture was serum from a person with syphilitic chancre; later, serum from (1) a secondary syphilitic lesion (papuloerosive or condyloma) and (2) circulating blood (from early syphilis). While positive results were obtained from these serums, best results were obtained through hemocultures. In this process, T. pallidum is found mostly beneath the surface. To reach maturity, T. pallidum has to pass the following stages: (*a*) granules which are three together or four together; (*b*) rods which are like narrow sticks; (*c*) mature treponemes. It is emphasized that the only way to develop treponemes is through the development of the granule—not by breaking two pieces of a treponeme.

Studies on Biphasic Hemolysin in Rabbit Syphilis.— Wicher and Rogala [39] found that the Donath-Landsteiner reaction was negative in 68 syphilitic rabbits in the first year after infection with the Nichol's strain of T. pallidum. Thirty rabbits were exposed to the action of low temperatures; in 10 both ears were treated with chlorethyl; 10 were closed in a refrigerator at 4 C, and 10 were given injections intravenously with saline cooled to 0 C. In all animals the Donath-Landsteiner reaction remained negative.

Experimental Mouse Syphilis.—It has long been known that T. pallidum may

reside in organs of mice many months without losing its virulence. Berlinghoff [40] studied the Nelson test in such infected mice. The test always gave negative results, although portions of the mouse organs were capable of infection in rabbit testicles and produced typical chancres. In the rabbits the Nelson test then became positive. The immunity in mice is different from that of man and of rabbits.

Cutaneous Allergy in Syphilis.—Banque and Baseilhac [41] studied the reponses of the skin of syphilis patients at different stages of the disease after introduction of formal suspension of Borrelia hispanica. The preparation of the antigen was described in detail. The results showed that syphilis patients who reacted positively intracutaneously to a suspension of Nichols strain of the treponeme frequently reacted positively to a suspension of the B. hispanica but that, in addition, reactive results were obtained in primary syphilis with the latter, whereas the treponeme (Nichols) suspension yielded only nonreactive results at this stage. The investigators are trying to isolate the reactive fraction.

The technique for the preparation of purified antigen extracted from pathogenic treponemes suitable for animal inoculation, as well as the difficulties encountered in assaying the antigen, are described by Thivolet and Simeray.[42] The technique for performing the test was also included in the paper, and the macroscopic and microscopic aspects of the reactive test results are described. The results of 588 tests are reported. They show excellent specificity and very good sensitivity of the test in tertiary syphilis, in visceral syphilis in all its forms, and in congenital syphilis but not in neurosyphilis, in "serologic" syphilis, or in treated syphilis. Chemical analysis revealed that the reactive agent is probably a protein fraction of the treponeme. Tests were made for specificity with yaws treponemes and recurrent spirochetes. The reaction is discussed with reference to the course of its positivity and the concommitant course of the disease itself.

Effect of Novobiocin in Experimental Syphilis.—With growing frequency the physician encounters the problem of choosing a therapeutic agent for syphilitic patients who are sensitive to penicillin. Therefore, Garson and McLeod [43] studied the effect of novobiocin on syphilitic rabbits. Syphilitic rabbits injected with novobiocin in aqueous solution for five to eight days showed disappearance of lesions when treated with daily doses of 300 or 30 mg. per kilogram. However, the animals receiving the 300 mg. dose subsequently died as a result of treatment, and those receiving the 30 mg. dose relapsed within five weeks. A daily dose of 1 mg. per kilogram appeared somewhat to enhance the infection. In another experiment, Garson and McLeod administered novobiocin in Upjohn diluent USA, a vehicle said to increase and prolong the levels of this antibiotic in the blood. The syphilitic rabbits were treated with daily doses of 120, 60, or 30 mg. per kilogram and became asymptomatic by the end of treatment. All the animals survived and no relapses occurred during a period of five weeks. The investigators are planning to continue their observations of this experiment.

Effect of Cortisone in Experimental Syphilis in Rabbits.—Schmidt and his coworkers [44] studied the effect of cortisone in rabbit syphilis. Cortisone, 25 mg., was given intramuscularly daily for 14 days with tapering off for a subsequent 6 days to one small group at the time of inoculation, to another small group 3 weeks after inoculation, and to another group 5 weeks after inoculation. Four reagin serologic tests were carried out twice a week for 100 days and quantitative TPI tests were performed on selected sera. In the group in whom treatment was started at the time of inoculation, the rise in reagin titer was delayed, the maximum titer being reached 10 to 14 days later than in the controls. In the group in whom cortisone was started three weeks after inoculation, the titer declined when cortisone was started but rose again after it was terminated. There was no demon-

strable effect of cortisone on the TPI titers in any of the groups. Clinically the orchitis was delayed in onset and remained slight in most of the animals in whom treatment was begun early. A pronounced increase in size of lesions was seen in most of the animals in whom treatment was started late. In the dosage employed, cortisone showed a definite toxic effect, causing loss of weight, reduced appetite, dull fur, and apathy. It was pointed out that the fall in antibody titers might be related to the poor general condition of the animals during cortisone treatment.

Action of Various Penicillin Preparations on T. Pallidum.—Viaseleva [45] discussed the action of various penicillin preparations on T. pallidum. In Part I he reports his study of the action of penicillin on cultures of T. pallidum. Cultures of five strains were used as were various penicillin preparations. From these experiments the author concludes: 1. By the short-term action of penicillin high concentrations are necessary to produce cessation of motility and changes in morphology. 2. Cessation of motility and partial deformation do not necessarily mean the Treponema has died, subcultures may still be obtained. 3. By prolonged action of penicillin, the minimum spirochaetostatic dose to produce an antispirochetal effect was an average of 0.015 to 0.039 units per milliliter, the maximum (verging on the spirochaetocidal) averaged 1.84 to 3.16 units per mililiter. 4. Among the penicillin preparations, the minimum spirochaetostatic dose of Ecmonovocillin was among the smallest. An 0.25% solution of Ecmolin rendered 50%-75% of treponemes nonmotile; the addition of 0.5%-0.7% of Ecmolin completely inhibited the growth of T. pallidum. Part II [46] deals with the change in morphology of T. pallidum in culture and attempts to adapt it to penicillin. The experiment was done in the laboratory of electron microscopy of the Institute of Epidemiology and Microbiology of N. F. Gamaleia Academy of Medical Sciences of the U. S. S. R. with T. pallidum (Strain VII) in culture. Morphological changes (varying according to the concentration of the preparation in the nutrient medium) were produced under the influence of penicillin and studied with the electron microscope. Treponemes were grown on Tarozzi medium containing penicillin in amounts from 0.01 to 0.66 per milliliter. Seven figures illustrating various forms of the treponemes are included. Treponemes grown in media not containing penicillin were studied also.

Test of Possible Activity of Antibiotics in Syphilis Using Reiter Treponeme.—Mutermilch and Gerard [47] compared the sensitivity of the Reiter treponeme to the principal antibiotics and compared that of other strains of T. pallidum. Tests were performed in tubes containing serial dilutions of the antibiotic being tested. For penicillin, the bacteriostatic dose for the Reiter strain was about 0.3 I. U., or 0.18μg. The bactericidal penicillin dose was 600 I. U. The bacteriostatic dose for Reiter strains for erythromycin was about 0.37μg., and the same for carbomycin (Magnamycin). For oxytetracycline (Terramycin), 0.6μg. proved bacteriostatic for Reiter's treponeme; 1.5μg. for tetracycline; 6.25μg. for spiromycin (Rovomycin); 25μg. for chloramphenicol and the same for chlortetracycline (Aureomycin); 12.5 units for bacitracin; Reiter's strain showed resistance to streptomycin, to Framycin (Framycetin Sulfate), viomycin, Polymycin, and tyrothrycin. Suitable bacteria, such as staphylococci and Bacillus subtilis, were employed as controls. These findings are similar to known findings with other strains of T. pallidum and to results of treatment of syphilis with these antibiotics, when they have been so used. An experiment that was successful in treating syphilis in rabbits with spiromycin is described. The conclusion is that because their sensitivities are similar to the various antibiotics, the Reiter treponeme may be substituted for the dangerous T. pallidum in testing the treponemicidal activity of new antibiotics.

Influence of P^{32} upon Antibody Titer of Latent Syphilis.—Subsequent to a brief preliminary report in 1954 noting the

serologic fluctuations in patients with latent syphillis when given P^{32}, an experiment was made by Nakajima and Hayashi,[48] using four persons with congenital syphilis, one with early syphilis, and seven with late syphilis. All patients had been given various antiluetic therapy unsuccessfully. Previously 0.5 mc. of P^{32} was used; in this experiment the amount of the drug was doubled (adults, 1 mc. and children 0.5 mc.). For use in the experiment, 5 mc. of P^{32} in a solution of $H_3P^{32}O_4$ diluted in sterile distilled water to contain 1 mc. in 2 cc. was stored in ampules. Marked fluctuation was noted in the entire series with no untoward reaction. In the previous report, one case presented reactions which were assumed to be biotropism induced by the function of P^{32}.

Influence of P^{32} upon Antibody Titer of Late Rabbit Syphilis.—P^{32} was given by Mizumoto and Hayashi[49] to 14 rabbits which had been inoculated with T. pallidum 100 days before (10 of these were given both P^{32} and penicillin) in an attempt to corroborate results previously obtained in individuals with latent syphilis when given P^{32} following unsuccessful antisyphilitic therapy. The investigators discuss the experiment and include tables showing changes of seroreaction following administration of H_3PO_4, penicillin, P^{32}, and P^{32} followed by penicillin. They concluded that P^{32} administered intravenously definitely causes fluctuation in the seroreaction of rabbits with late syphilis.

Diagnosis of Syphilis

The chief concern in the literature of this review period with respect to the diagnosis of syphilis has been in the field of serology. This is not unlike the situation in previous years. There are two main lines of inquiry: (1) the present status of the serologic tests and (2) the continued study of the new tests. The latter effort is of more and more importance to the general diagnostic problems involving biologic false reactions.

Serodiagnosis

Doepfmer[50] reviewed the present status of the classical syphilis serodiagnostic procedures. Teague,[51] too, reviews in a concise manner the present status of serologic tests for syphilis. He warns against the tendency to jump on the false-positive band wagon too quickly and thus take the chance of doing the patient a grave injustice. He recalls that the Venereal Disease Research Laboratory (VDRL) microflocculation slide test has proved itself to be the most sensitive and the most specific of the nontreponemal tests. Significantly fewer biologic false-positive reactions result from this test when properly performed than from any other. An example of the greater specificity of the VDRL test was shown in 13 nonsyphilitic seronegative volunteer prisoners who were experimentally infected with Plasmodium vivax malaria and whose subsequent blood tests for syphillis were performed at a time that had been predetermined to be that at which the greatest number of false-positive reactions to tests for syphilis would be produced. The false-positive rate in this group ranged from 82.3% for the Kahn to as low as 3.8% for the VDRL slide test, intermediate values being obtained with the Kline and Kolmer tests. An equally impressive example of the greater sensitivity of the VDRL is the detection of small amounts of reagin in the sera of patients who have been adequately treated for syphilis and who are seronegative with other serologic tests. Since the opening of the Cleveland Clinic, in 1921, serologic tests for syphilis are part of the routine laboratory examination of all new patients and any former patient for whom complete reexamination is requested. King and Reich[52] believe that routine serologic tests for syphilis are useful. After considering a representative sample of 12,396 blood specimens that were submitted to their laboratory in a four-month period, they feel that not only are many cases of previously undiagnosed syphilis found, but attention is focused on many previously diagnosed cases, some of which require more adequate treatment. Some patients are inaccurate in answering questions about a possible history of venereal disease, and some, even in the presence of unmis-

takable clinical evidence, will admit to having a history of syphilis only after a positive serologic test has been reported to them. The usefulness of the premarital blood test seemed to be slight in the population served (not a cross section but heavily weighted by a large number of professional people and their families).

Technical Considerations

Complement Fixation with Erythrocytes of Polar Deer.—Demchenko [53] found that polar deer erythrocytes gave a fairly good substitute, in the Russian far north, for guinea pig and sheep in the performance of the complement-fixation test.

Examination of Badly Hemolyzed Blood Specimens with VDRL Test.—In the routine testing of blood sera with the Kahn and VDRL serologic tests for syphilis, an occasional blood specimen is received through the mails which is too badly hemolyzed to give satisfactory readings with the Kahn test but which gives definite reactions with the VDRL test. Lawler developed a method for treating these hemolyzed specimens so that they could be examined with the Kahn test, but the method is too cumbersome for routine use. The Kahn and VDRL tests were used by Nagle and Welch [54] on 1,056 nonhemolyzed blood specimens. The results were compared with the VDRL test results on the same specimens artifically hemolyzed. The comparison indicated that negative results obtained with the VDRL test on sera too badly hemolyzed for a satisfactory Kahn test appear to be dependable for reporting to physicians.

Cardiolipin Antigen

Concentrated Solution of Lecithin in Kahn Antigen.—In a detailed presentation, McDermott, Nakamura, Dockrill, and Kahn [55] point out that certain lipid extracts used as antigen in the Kahn test, when mixed with salt solution, present heavy, nondispersible lipid aggregates which make the suspension unsatisfactory. It was found that addition of a small amount of a concentrated solution of lecithin readily corrected this difficulty. The investigators believe that these aggregates are due to the presence of an excess of cardiolipin or a cardiolipin-like substance in relation to lecithin.

Saturated Synthetic Lecithins in VDRL and Kolmer Antigens.—Tonks and Allen [56] studied three pure synthetic lecithins incorporated in cardiolipin antigen. The dimyristoyl lecithins were found satisfactory in serologic testing; the sensitivity of the antigen could be adjusted to the desired level merely by increasing or decreasing the concentration of the lecithin. Dimyristoyl lecithin is stable for at least a year in solid form and in alcoholic solutions. Reproducibility of results utilizing different batches of these synthetic lecithins has not been attempted as yet, but if studies are satisfactory, the synthetic lecithins may spell an advance in serology in view of their ease of handling and their stability.

Comparative Slide Tests with Cardiolipin Natural Lecithin Antigen and Cardiolipin Synthetic Lecithin.—Since the indentification by Pangborn, in 1941, of cardiolipin and lecithin as the active constituents of the lipid tissue extracts used as antigens in the serological diagnosis of syphilis, numerous investigators have shown that antigens prepared with the purified reagents in optimum proportions give better results than do the original preparations. However, while natural cardiolipin extracted from beef heart is of constant potency, preparations of lecithin from the same source are more variable. Levine, Kline, and Stephens,[57] in an attempt to overcome this difficulty, prepared synthetic lecithin by the method of Baer, and 6,162 comparative slide tests were carried out on routine combinations of cardiolipin with this synthetic product and with natural lecithin. In reactive tests 97.7% agreement was obtained between the two combinations, while 99.57% agreement was observed in nonreactive tests. The investigators therefore favor the use of the synthetic lecithin, different lots of which have a constant optimal ratio with cardiolipin, making for greater use of prepara-

tion of the antigen mixture. They point out that it is the general opinion at present that the majority of false-positive serological reactions are due to technical defects in the naturally prepared antigens, rather than to biological abnormalities in the patient.

Vegetable Antigens for Wassermann Test.—Medical Science [58] reports that an article by Dr. L. S. Reznikova, of Moscow, published in the *Vestnik Venerologii i Dermatologii* (December, 1956), described experimentation with antigens produced from such vegetable sources as wheat, soya beans, potato flours, almonds, walnuts, and the legume arachis. Dr. Reznikova found that vegetable antigens contained phospholipids, although these were present in smaller amounts. Lecithin was absent. Antigens were prepared from a mixture of vegetable and animal extracts and used in the Wassermann tests. They showed high sensitivity, with the highest achieved with almond antigen (98.4% as compared to results with purely animal extracts) and soya-bean-flour antigen (97.9% correlation). Results with potato-flour antigens were only 90.7% accurate. This work confirms the 1923 study of vegetable extracts in the Wassermann test by Weiss.[59]

Composition of Cardiolipin.—Rice [60] reports the results of a preliminary study in which cardiolipin was separated into a number of chromatographically distinguishable fractions each of which possessed the biological activity, as measured by the cardiolipin flocculation test, of the unfractionated cardiolipin but which differed in the fatty acid moiety.

Differentiation of Antilipids Occuring in Nontreponemal Diseases and Syphilis.—Kent and his co-workers [61] studied the capacity of cardiolipin-lecithin-cholesterol (C-L-Ch) antigens to react with antilipids of syphilitic and nontreponemal origin, as a function of the lecithin component. Concentrations of lecithin conferring, as nearly as possible, selective reactivity with syphilitic antilipid were demonstrated for two standard diagnostic tests—one a slide flocculation, the other a complement-fixation procedure. A simple slide-flocculation test for differentiating nonsyphilitic and syphilitic antilipids was developed on the basis that the former react maximally with C-L-Ch antigen of relatively low lecithin content (0.15%), the latter with antigen of high lecithin content (0.27%). Nonsyphilitic reactivity patterns were observed in 84% of patients with nontreponemal infections or disorders, syphilitic patterns in 95% of patients with syphilis.

Price's Precipitation Reaction in Serodiagnosis of Syphilis.—In 1,300 sera from known cases of syphilis in various stages, 35 sera from normal persons, and 670 sera from patients suffering from diseases other than syphilis, Darekar and Jhala [62] studied the Price Precipitation Reaction in parallel with Meinicke slide, VDRL, and Kahn tests. The Price Precipitation Reaction was found to have a higher specificity but a lower sensitivity than the other tests. However, the incidence of biologic false-positive reaction in various nonsyphilitic diseases was lowest with the Price Precipitation Reaction.

VDRL, Eagle, Price, and Kolmer Tests for Syphilis.—An evaluation of specificity and sensitivity of the VDRL, Eagle, Price, and Kolmer tests was done by Hill, Buckle, and Thomas. [63] They report that 100% specificity rating was reached with the Kolmer complement-fixation test at 2 dilutions, the VDRL and Price Precipitation Reaction at 16 dilutions, and the Eagle flocculation test at a level of 32 dilutions. In a blood-donor series, the specificities were Kolmer 99.89% and VDRL 99.32%. All four tests showed a higher sensitivity rating in cases of untreated syphilis, but none was superior to the others in particular stages of the disease. It was concluded that there is no simple, highly sensitive "screen" test which can be used in country districts by laboratory aides.

TPI Test.—There is continued work in the direction of evaluation of the T. pallidum immobilization test. This takes the form of comparative studies, critiques of factors involved in the performance of the

test, and its adaptability to special circumstances.[64-66]

Durel [67] opposes the view expressed by Kolmer that the TPI test yields 8% false-positive results. He believes it is very difficult to prove this assertion, especially since the TPI test is the agent of reference in the diagnosis of the treponematoses. Garson [68] carefully reviewed and compared the current treponemal tests for syphilis. He included in his discussion such factors as availability, technique, results, and cost. Reproducibility, specificity, and sensitivity are considered in some detail.

TPI and TPCF Tests on 2,000 Patients Difficult to Diagnose.—Harris and his co-workers [69] reported that the results obtained with the TPI and TPCF (T. pallidum complement fixation) tests on 2,000 serums from diagnostic-problem patients were in agreement on 1,745 serums (87.3%). Of the 1,407 serums from patients listed as probable biologic false-positive reactors, 47% were nonreactive to both the TPI and the TPCF tests. Results from either test alone were in slightly closer agreement with the medical opinion than these specimens were from biologic false-positive reactors, since 54.3% nonreactive results were obtained with the TPI test and 52.0% were produced in the TPCF test. Of the 1,407 serums, 40.3% were either reactive or weakly reactive in both the TPI and TPCF tests. The group of specimens from females showed closer agreement with the medical opinion than specimens from males. Nonreactive results were produced by TPI in 58.8% and by TPCF in 55.5% of the serums from female donors, whereas each test produced nonreactive results in 45.5% of the serums from males. This may reflect some factor, present in the female, that is responsible for an increased percentage of BFP reactions.

TPI Test in Far East.—The TPI test was established successfully in the Far East by Muschel, Blumberg, and Gelsing.[70] From a technical point of view the only serious difficulty encountered in establishing the test in Japan was the requirement for a mixture of nitrogen and carbon dioxide gas. Those obtained from Japanese sources were toxic to treponemata, making it necessary to import gas mixtures from the United States. These observers could not demonstrate that the Orientals tested had any particular predilection for biological false-positive, at least as compared to the Americans similarly tested.

Survival Medium for T. Pallidum Utilizable for TPI Test.—Disadvantages of the survival medium used by Nelson are that it does not keep well and requires rare products not easily obtained in Europe. Modifications have been tried by others with the aim of overcoming these disadvantages. Vincent,[71] after trying such things as human ascitic fluid, spinal fluid, and inactivated neutralized serum with reducer added, hit upon bovine amniotic fluid, which is isotonic, neutral, and easy to get and keep. It forms the base of his medium with a reducing system close to that of Nelson. In this medium T. pallidum survives at the rate of about 90% for 24 hours, 77% for 36 hours. Medium may be preserved for more than six months. Inoculation reactions are the same as those for Nelson's medium. Fifty sera tested with both Nelson-media-prepared TPI and bovine-amniotic-fluid-prepared TPI gave comparable results. The test is easier to read with the amniotic medium.

Kinetics of TPI Reaction Under Improved Conditions.—Portella and Thompson [72] present a number of modifications of the technique of the TPI test, aimed at lessening the tendency to clotting and lessening anticomplementary activity of the treponemal suspension. Extraction of treponemes from the testicular tissue at lower temperature, separation from most of the testicular tissue juice, and resuspension in a modified Nelson's medium permitted survival of 90% or more of the treponemes in the controls for 48 hours. Sensitivity of the test varies proportionally with the concentration of complement and with the square of the reaction time. Toxic or anticomplementary sera may be satisfactorily

tested by prolonging the incubation period and diluting the serum. Bioassay, with use of a reference-standard serum, is recommended.

Investigations on Reproducibility of Quantitative TPI Test.—After describing a special experimental plan and the associated technical conditions, Nielsen [73] reported his results on the reproducibility of the quantitative TPI test. Using the same complement and the same suspension of treponemes, the standard deviation of duplicate titrations of the same pool was estimated at 22%. With use of the same complement but different suspensions, the standard deviation of repeated titrations of the same pool was estimated at 52%. The contribution to the variance due to the employment of different suspensions of treponemes is about two-thirds of the total variance. Nielsen discusses the causes of the various contributions to the variance, and he further suggests the indications for investigations which might lead to an improvement in the reproducibility of the quantitative TPI test, along with methods for possible improvement of the qualitative routine investigations.

Treponemal Immobilizing Antibodies in Syphilis.—Fribourg-Blanc [74] suggests that some irregular results with the quantitative TPI tests may be due to an anticomplementary effect of the serum being tested, which partly destroys the immobilizing fraction of the complement but leaves sufficient hemolytic activity to lyse the test dose of cells, thus giving a falsely low reading. He uses three times the dose of complement to avoid this. Resting forms of treponemes may develop in rabbits under adverse conditions of temperature and other technical factors. These forms may produce irregular results. He avoids this by using only rabbits which develop orchitis within 10 days after inoculation. He believes the persistence of immobilizing antibodies in late or latent syphilis, even after treatment, is due to foci of resting forms which have temporarily become avirulent but continue to act as a stimulus to the production of antibody.

TPI-Negative, Routine Serologic-Positive, in Long-Term Case of Syphilis.—A case presented by Perkin and Herrmann-Fournier [75] concerns a 50-year-old woman who was first found to have syphilis in 1918, at the age of 10 years. It is presumed that it was congenital syphilis. Treatment of an unknown nature was administered then. The Wassermann reaction was reactive. It was still reactive in 1947 on routine examination. Treatment was administered in the form of a series of Bivatol, a series of Quinby, and a series of 10,000,000 units of penicillin, after which the Wassermann test became nonreactive. A series of tests (Kahn, Kline, Kolmer) and the TPI were performed after a lapse of five years with equivocal results. The patient was again treated, this time with 15,000,000 units of penicillin. After this, the TPI test became nonreactive, but the Kolmer, the Kline cardiolipin, and the Kahn standard and quantitative remained reactive. This is still the status quo. The obvious questions are formulated as to the wisdom of stopping treatment in face of a nonreactive TPI, etc. As regards the value of the TPI, this is the exception that proves the rule. In a discussion, Durel used this case to point out the doctrine that no case in which the TPI is nonreactive should be diagnosed as syphilis until all other factors that disturb serum proteins from their normal behavior are eliminated.

Comparison of Standard Tests for Syphilis with TPI Test.—Chorpenning and Beers [76] collected 183 cases from the U. S. Armed Forces in Europe, presenting a problem of differentiation between latent syphilis and a biologic false-positive reaction. These cases were retested by the STS and examined by the TPI test. The incidence of BFP reactors when screening of asymptomatic "seropositive" cases was performed with cardiolipin was less than when screening was done with other antigens.

TPI and TPCF Tests.—Comparison of the TPI and TPCF tests was reported by the men performing these tests for the Ohio Department of Health.[77] They feel that

with the TPI procedure being so complicated, time-consuming, and expensive, the TPCF test has potentiality of replacing other T. pallidum tests. They found that 64% of the 92 cases reacted positively in the two treponemal tests (TPI and TPCF), or in agreement with the original positive standard serologic tests for syphilis.

Comparison of Several Serologic Tests for Syphilis with Use of T. Pallidum Antigen.—Falcone and Harris [78] discussed the results obtained from several different testing procedures using T. pallidum as the antigens, with serums from 28 syphilitic patients and 200 persons diagnosed as probable biologic false-positive (BFP) reactors. The patients, located in 30 states, probably represent a fair cross section of diagnostic problems in syphilis seen by the average physician. Test methods are described, including the following tests: TPI, T. pallidum agglutination, T. pallidum immune-adherence, T. pallidum methylene blue, and TPCF. Roulin and Baelden [79] feel that the complement-fixation test is very close to the Nelson test as regards sensitivity and its use reduced the usual divergence between the results of the classic serologic tests and those given by the Nelson test. The difference between the two tests may be in favor of the Nelson procedure but also more often in favor of the fixation test. The Nelson test becomes negative first during the treatment of early syphilis. The Nelson test is more specific, since the fixation test gives some false-positive reactions.

TPCF Test

Garson and Portnoy [80] state that the TPCF test has provided another serologic tool to aid in the diagnosis of syphilis and for the differentiation of the biologic false-positive reactor. It seems to have a greater value in confirming a diagnosis of early syphilis than does the TPI. The sensitivity of the TPCF test in early syphilis is at least as high as the conventional tests for reagin. However, the agreement between the two treponemal tests is not absolute, although complete agreement was almost attained in the probable biologic false-positive group. The good reproducibility of the TPCF qualitative test thus far observed is undoubtedly due to the use of standardized antigens and the persistence of stabilized TPCF antibody titers in treated latent syphilis over the two-year period of observation. The present cost of the TPCF test precludes its routine use in the follow-up of treatment.

Guyon and Cole [81] studied 164 cases in which the results of the standard Kahn test and TPCF test were correlated with clinical studies. The agreement of results in untreated syphilis was excellent, and to less degree in treated cases. The greatest difference in test results appeared among the false-positive reactors (32 cases). This disagreement might well have approached 100% had the original reactive sera been available for TPCF testing.

In comparative studies with the TPCF and TPI tests, employing aliquots of serum specimens from 394 cases of possible latent syphilis or biologic false-positive reactors, the Michigan group [82] obtained 92% agreement. The nature of the disagreement indicates that the TPCF test is less sensitive than the TPI test for specimens obtained from these two clinical groups. With use of two different experimental conditions, the TPCF test results were reproducible in 93% and 95% of instances of duplicate testing. Reproducibility of results was less satisfactory if aliquots of sera were tested simultaneously with two different antigens than if such aliquots were tested on different days with the same antigen.

Cannon [83] described a family with a biological false-positive test for syphilis. Although the size of the family and the number studied are too small to draw conclusions as to the hereditary pattern or type of transmission, Cannon did note that all the positive members were females and that the males were consistently negative. The positive reactions were of low titer. The test results varied from time to time in the members who showed a positive reaction. The TPCF test may be positive in

female members whose standard serologic tests are negative. The TPI test is indicated where the TPCF is positive because in this family the TPI proved to be consistently nonreactive, thus bearing out the clinical diagnosis of a biologic false-positive test. The electrophoretic study showed a normal protein distribution pattern.

RCPF and TPIA Tests

Rein and his associates [84] reported a cooperative study based on a series of 1,055 serum specimens subjected to examination with complement-fixation tests employing pathogenic T. pallidum (TPCF) and nonpathogenic Reiter treponeme (RPCF) protein extract antigens. Their preliminary investigation indicates that the Reiter protein extract antigen employed in their study has a sensitivity and a specificity comparable with the TPI, TPIA, and TPCF antigens. DeBruijn [85] also did a comparative study on the complement-fixation test, using a protein fraction derived from T. pallidum (Reiter strain) as an antigen, and the TPI test. He tested 116 syphilitic and 137 presumably nonsyphilitic sera. The complement-fixation test with protein antigen showed an excellent sensitivity, together with a satisfactory specificity. Gastinel and his co-workers [86] studied the Italian soluble preparation of the Reiter treponemal protein (ATPS). It has proven to be more sensitive than the pallida-antigen or the usual antigen. It is less sensitive than the TPI. It can be used intradermally in determining the state of senitization of rabbits prepared with the Reiter treponeme. It also evokes strong reactions in syphilitic rabbits after 55 to 880 days, but it is without effect in specific patients, giving a feeble (questionable) response to the Luotest. Ruge and his associates [87] feel that the new pallida-antigen is a worth-while enrichment in the serodiagnosis of syphilis. It yields a group specific measurable supplement for the serologic picture and implies that a repeated positive pallida reaction has greater possibility of there being an underlying syphilitic process.

Vaisman and his group [88] found that an antigen obtained by the disintegration of T. pallidum by means of ultrasonics, employed in complement-fixation reaction, presents great interest in the serodiagnosis of syphilis, with greater sensitivity and specificity than the lipoidal antigens and those of the Reiter strain without reaching the value of the TPI test. The antigen used by Pautrizel and his co-workers,[89] of the Faculty of Medicine, Bordeaux, is prepared by growing bulk cultures of the Reiter treponeme anaerobically for nine days in thioglycollate broth with added rabbit serum, the organisms being then separated by centrifuging. After being washed several times in saline the treponemes are suspended in a small volume of 0.3% phenolsaline and disintegrated by exposure to ultrasonic waves. After further centrifuging at 2,000 rpm for 10 minutes to remove gross particles, the supernatant fluid constitutes the antigen, which is stable for up to two years when stored at 6 C. It has been used in the Kolmer complement-fixation test, the stock antigen being further diluted in 1 in 10 parts of saline before use. It is said not to be anticomplementary. Serial tests were carried out on sera from rabbits which had been infected by intratesticular inoculation with the Nicholas strain of T. pallidum, some animals being left untreated, others given a curative dose of penicillin after 3 to 5 weeks, while a third group were treated 4 to 12 months after infection. The behavior of the antitreponemal (A-T) antibody was compared with that of reagin, as shown by the Kline and Kolmer tests. The A-T antibody was often found to develop earlier and rise more rapidly in titer than reagin. When the rabbits were treated early in the infection, the A-T antibody titer fell rapidly and indeed disappeared. Lysed and intact organisms may detect different antibodies which are distinct from reagin and immobolizing antibody.

The T. pallidum immune adherence (TPIA) test has obvious advantages over the TPI procedure in that killed treponemes are used as antigens. They may be stored

under refrigeration for many months and be made available to laboratories that do not have adequate facilities to cope with the technically more complicated TPI test. Many problems have been encountered in dealing with methods for the preparation and preservation of TPIA antigens. Rein and Kelcec [90] reported their experience with a phenolized antigen. They found that TPIA antigens preserved with 0.25% phenol remained uncontaminated for a period of more than a year. On the other hand, phenol seemed to alter the surface of the treponemes in such a manner that they would cross react with unspecific reagin. It was found necessary, therefore, to absorb this reagin with a cardiolipin-lecithin antigen prior to testing with the TPIA procedure. This absorption procedure did not affect the specific antibodies that were detected by the phenolized TPIA antigen.

Cain [91] believes that an agglutination test, with use of procedures he outlined, can be successfully employed in the serodiagnosis of syphilis with a high degree of sensitivity and specificity and with a minimum of difficulties encountered when compared to current diagnostic laboratory procedures. Antigens that would not spontaneously agglutinate or agglutinate in normal saline and normal human or rabbit serum, were successfully produced by using rabbits pretreated with either cortisone acetate or roentgen-ray irradiation. Complicated media are not required for the agglutination test since the maintenance of life of the treponemes is not involved as in the immobilization test. The results of the agglutination test are easy to read in that the presence or absence of agglutinated masses establishes the presence or absence of antibodies and such results are not dependent upon numbers of organisms remaining alive, particle size, or reduction in opacity as are some of the current serological methods. This is an experimental paper and the actual sensitivity and specificity is not adequately determined.

Antigenic Structure of T. Pallidum.—Results of a study by Hardy and Nell,[92] made to determine the cause of various inconsistencies obtained with treponeme suspensions prepared at different times, indicate that T. pallidum has a complex antigenic structure and that the activity of these different antigenic components causes the observed inconsistencies.

Rapid Plasma Reagin Test for Syphilis.—Portnoy, Garson, and Smith [93] point out the desirability of a serologic test for syphilis, the results of which would be available within a few minutes. It would be useful for "on the spot" serologic testing when large numbers of persons must be tested quickly. It would be of value also in any population group where follow-up is difficult. Plasma and serum specimens from 1,609 patients were tested. Sedimented slide-test antigen emulsion was suspended in 10% choline chloride as used in the plasma test. Blood specimens were centrifuged at room temperature, and the plasma was tested without heating. Mixtures of plasma and antigen were put on a mechanical rotator for four minutes at 180 rpm and tests were read microscopically immediately. The Rapid Plasma Reagin (RPR) test was consistently more reactive than the Venereal Disease Research Laboratory (VDRL) test on serum. In 51 of the 1,609 cases the RPR test was reactive to some degree when the VDRL test was nonreactive. Of these 51 patients, 45 (88%) gave a history of treated syphilis. This is a preliminary report. However, the RPR test for syphilis was used in California in 1957 as part of the program of examining Mexican farm workers entering the United States. At the reception center 47,579 workers were tested. Blood specimens were examined and differential diagnoses were completed on the spot. Workers with syphilis were treated and contact information was obtained before they left the center. Of the 47,579 tests, 3,913 or 8.2% were reactive, and an additional 685 were weakly reactive. Among the reactors diagnosed as syphilitic were 31 primary and secondary cases, 985 early latent cases, and 2,712 latent. It was believed

that the results of the RPR test compared favorably with those of other nontreponemal and treponemal tests done on a sample of about 1,600 specimens.

Interpretation of Seriologic Reactions (Biologic False-Positive Reactions)

Many attempts have been made to set up useful guides for the physicians to help them evaluate seroreactions.[94] This whole effort is tied up with the false reactions to the serodiagnostic tests.

In the Thomas P. Murdock Memorial number of the *Connecticut State Medical Journal* a nostalgic article,[95] reprinted from the *American Journal of Syphilis* (January, 1930), reports on the value of obtaining blood Wassermann reactions routinely on private patients and discusses results in 2,500 Wassermann reactions from 1,942 patients. Five per cent of the patients examined had reactive test results. At the time the article was written, 57 (of the total 106 patients found with reactive test results) were known to be living, and 18 of those had syphilis of the central nervous system. Other statistics are discussed and the following conclusions were reached by the authors: 1. Routine blood Wassermann tests are justified if even a small percentage of reactives are found. 2. Syphilis is declining. 3. Neurologic syphilis is more frequent than most physicians believe. 4. Only a small percentage of syphilitics are serologically nonreactive. In contrast to Murdock and Hall's report, Beerman[96] reviewed the significance of a positive serologic test for syphilis today. When syphilis was prevalent, all positive serologic tests for that disease were usually considered to signify syphilis; now, with a lower prevalence, the false-positive reaction takes on more significance. A number of factors must be considered in connection with false-positive reactions: serologic reactors; type of nonsyphilitic disease; incubation period for the development of false-positive serologic reactions; number of tests employed in a serologic battery; types of tests; intervals of testing, and duration of false-positive reactions. Biologic false-positive reactions are now considered as acute or chronic. Acute reactions disappear spontaneously within a few days, weeks, or months, and are usually associated with a bacterial, viral, plasmodial, or rickettsial infection. The chronic reaction may exist many months or years, even for a lifetime. The only infectious disease known to produce chronic biologic false-positive reactions in a high proportion of cases is leprosy. A proportion of patients with collagen diseases may show chronic biologic false-positive reactions. The chronic biologic false-positive test may be the first manifestation of a collagen disease. The clinical recognition of biologic false-positive reaction is a time-consuming and laborious procedure. For any suspected biologic false-positive reactor there should be epidemiologic investigation, careful history and physical examination, cerebrospinal fluid study, tests for malaria and infectious mononucleosis, L. E.-cell test, and the more specific tests for syphilis, such as the TPI test.

Chronic BFP.—Of 245 patients with persistent biologic false-positive reaction, Miller, Brodey, and Hill[97] found systemic disease in 23.2%. Females accounted for 71% of the total series and 84% of those with systemic disease. The known onset of the biologic false-positive reaction reached its highest incidence in persons from 20 to 30 years of age. The presence of a biologic false-positive reaction manifested only by a positive Mazzini test is valid. Two per cent of the total series have developed systemic lupus erythematosus, and an additional 13% could loosely be classified as having lupus diathesis. One-third of patients with biologic false-positive reaction with no apparent clinical illness were found to have one or more positive laboratory findings indicative of abnormal globulins. A minimum laboratory examination on all biologic false-positive reactors should include determination of the sedimentation rate, cephalin-flocculation and thymol-turbidity tests, and protein partition. Cowan,[98] too, has stressed the importance of the chronic biologic false-

positive reaction both as to its diagnostic significance in connection with the so-called collagen diseases and with the state premarital examination law which requires that persons with positive or doubtful serologic reaction must have a special medical dispensation before they can marry in the state of Michigan. The TPI test, valuable as it is, is not considered a practical solution to the problem because of the expense and the time required to obtain test results. Development of other tests, such as the TPCF test, is highly desirable. General observations from conclusions of investigators in this field are included as follows: 1. There is a probable margin of error of 2% or less in the results of the TPI test. 2. It is frequently first discovered by routine blood testing of apparently healthy persons. 3. It is twice as frequent in women as in men and more frequent in younger persons of both sexes. 4. It is frequently followed (in a few years) by verified systemic lupus erythematosus (SLE) or an episodic form of chronic illness with manifestations conforming to those of SLE. 5. It frequently is accompanied by hematologic disorders and associated with disorders of serum globulin. A biologic false-positive reaction is not an end-point but rather the starting place for clinical investigation of the patient for nonsyphilitic diseases. Results of the VDRL and cardiolipin Kolmer tests in cases requiring a differentiation between latent syphilis and a chronic biologic false-positive reaction are discussed and compared by Chorpenning and Beers [99] with those of the TPI test and with clinical findings. Of a total of 183 cases, 39 (22.5%) were negative by the TPI test. Only 3 of these 39 cases had clinically recognizable diseases, and all were reactive to the STS. Results indicate that a large number of the false-positive cases studied were "chronic" BFP reactors and BFP reactors occurred less frequently when screening of asymptomatic "seropositive" cases is done with cardiolipin than when done with other antigens. The Kolmer complement-fixation test does not have sufficient sensitivity and is not recommended for sole use as an exclusive procedure since approximately 15% of latent syphilis cases could be missed by such a procedure.

Hypergammaglobulinemia, Circulating Anticoagulant, and Biologic False-Positive Wassermann Reaction.—A study was made by Laurell and Nilsson [100] of the sera from two patients with hypergammaglobulinemia whose sera contained circulating anticoagulants with antithromboplastin effect and showed biologic false-positive reactions to serologic tests for syphilis in an effort to determine if the anticoagulating effect and the positive reactions with lipid antigen were ascribable to one and the same causal factor. With electrophoretic fractionated sera, the Wassermann reagins and the antithromboplastin were localized in the γ-globulins. Upon absorption with lipid antigen, both the Wassermann reagins and the antithromboplastin could be removed from the active, separated fractions; neither could be removed from unfractionated sera. The antithromboplastin activity decreased by approximately 50% with thromboplastin absorption of unfractionated sera; and the titer of the Wassermann reagins remained unchanged.

Relative Specificity of Serologic Tests for Syphilis in Mycobacterium Leprae Infection.—Antibodies that react with cardiolipin antigen are known to develop in persons who are infected with Mycobacterium leprae and such antibodies cause reactions in serologic tests for syphilis. The specificity of serologic tests for syphilis was evaluated by Kent and his colleagues [101] in a study of serums from 34 nonsyphilitic patients with infections caused by M. leprae. The serums were processed aseptically and air-mailed to Walter Reed Army Institute of Research in a container that was refrigerated with solid carbon dioxide. Seven tests were performed, some with more than one antigen. Among them were the following tests: four slide-flocculation tests (i. e., the VDRL, Kline, Rein-Bossak, and Mazzini); one tube-flocculation test (Kahn standard); two complement-fixation tests (Kolmer and CF52). The frequency of reactions varied

from 6 to 21 in tests with the lipoidal antigens that are present in ordinary extracts of tissue, and from 7 to 17 in tests with cardiolipin-lecithin-cholesterol antigens. The specificity of the cardiolipin antigens was correlated with their content of lecithin.

Positive Wassermann and Kahn Tests in Endocarditis Lenta.—Kaipainen and Seppälä [102] reported a positive or weakly positive serologic test for syphilis in 61 cases in their study of 221 patients with endocarditis lenta. In 11 cases (5%) the positive seroreaction was possibly due to syphilis; in only 1 case was endocarditis lenta found to have developed from a proved syphilitic valvular defect. In 50 cases (22.6%) the positive serologic tests for syphilis were considered nonspecific; in addition to a negative history of syphilis, this opinion was based on the autopsy findings, the great lability and mutual contradiction of the positiveness of the seroreactions, and the syphilis incidence of the hospitals (2.68% of 83,036 patients).

Cerebrospinal Fluid

Complement Fixation and Precipitation Tests for Syphilis on Cerebrospinal Fluid.—A comparative study was made by Chacko and his co-workers,[103] from India, of the VDRL tube precipitation test with cardiolipin antigen and the Kolmer modification of the Wassermann complement-fixation reaction with cardiolipin antigen on 489 specimens of cerebrospinal fluid. The materials and methods used are described, and the results are discussed and illustrated by four tables. Qualitatively, the two tests agreed in 95.6% of cases; quantitatively, no significant difference was noted in their titers. The VDRL spinal fluid precipitation test with cardiolopin antigen is considered to be equally as efficient as the complement-fixation test. It also requires a simpler technique and can be used as a routine test in all laboratories. The investigators suggest it be made the routine single test in laboratories throughout India.

Clinical Manifestations

The newer findings in clinical syphilology are not extensive. MacAlpine's [104] study of syphilophobia is outstanding. The bulk of the reports deal with late rather than early lesions of syphilis. In a most fascinating study of syphilophobia, MacAlpine presents 24 patients with this psychiatric condition and discusses incidence, psychiatric implications, clinical features, and treatment. She feels that the incidence of syphilophobia has not decreased with the decline in the incidence of syphilis. Men are much more often victims than women. All patients give a history of exposure to veneral disease, but this is frequently found to be delusional or fictitious (strange looks, drinking or eating from utensils that may previously have been used by a syphilitic, toilet seats, sleeping in strange beds, etc.). The patient's idea of exposure derives from and follows his delusional conviction of having syphilis. Suicide is a threat in many of these patients. The essence of management is sympathetic, patient, and extended history-taking in which the patient shares and the therapist says little. The physician should never reassure the patient that he does not have syphilis; the patient may interpret this as meaning that the doctor does not understand his case, that he does not have enough time to spend on him, or that he is lying. Such patients request repeated blood tests or treatment for syphilis. If these are given, the patient's delusion is strengthened as he feels that the doctor who ordered the blood test or treatment must at least have some suspicion that veneral disease is present. "A delusion shared by the doctor means a delusion very much reinforced by an unbiased objective authority." MacAlpine feels that the prognosis is often good and that not uncommonly delusions gradually recede under psychotherapy even without the development of insight.

Syphilis Transmitted by Blood Transfusion.—The first case of syphilis transmitted by blood transfusion in the medical literature appeared in 1915, and the first

general article, in 1928. Arturi and Usandivaras [105] believed that a reluctance to publish such instances accounts for the small number recounted in the literature. However, it has been estimated that over 2,000 cases have occurred solely in the United States. Since there is no sure way to eliminate the possibility of transfusing blood infected with syphilis when fresh blood is used, it is recommended that preserved blood only be employed except in cases of extreme urgency. The authors report their case of syphilis transmitted by blood transfusion.

Infection and Reinfection in Early Syphilis.—Prebble [106] reported a clear-cut instance of "ping-pong" syphilitic reinfection in a married couple. Felke [107] estimates that the relapse rate in early syphilis is less than 2% in patients with lesser promiscuity.

Latent Syphilis

According to the study of Curtis and Schuster,[108] of the University of Michigan, the decrease in the incidence of early syphilis has been accompanied by an increase in the proportion of latent syphilis to other forms of the disease. This makes the differentiation from biologic false-positive reactors all the more important, since both groups are relatively larger in the present population. They advise treatment for latent syphilis similar to that for early syphilis (4,800,000 units of penicillin G in oil and aluminum monostearate or 2,400,000 units of benzathine penicillin G). Seronegativity is not the goal of therapy. The TPI test is a better indicator of the immunological status of the syphilitic patient, after the test has once become reactive.

Late Syphilis

Grillmayr [109] discusses a latent form of syphilis, known as "island disease," in connection with the concept of Prof. A. Rottmann, of Vienna, that syphilis may be present even when the blood or cerebrospinal fluid is nonreactive. The syphilitic nature of this illness is established only by a reactive result from the Luotest repetition inoculation. These smaller syphilitic foci, known as "islands" (Grillmayr, 1954) may not always respond to the first Luotest repetition inoculation if they are very small and a second inoculation is of importance. Before determining a reactive blood test for syphilis as a biologic false reaction, the possibility of "island disease" should be considered. Six figures are included to illustrate the article, and general symptoms and treatment are discussed.

Sagher and Cohen [110] reported a clinical and laboratory comparison of 100 cases with a reactive serologic test which originated in two different geographic areas. Persia and Iraq, where a nonvenereally transmitted spirochetosis is endemic, contributed 49 cases of which only 16 were aware of their disease and had received treatment. The other 51 originated in Europe, North Africa, and Israel. Of these 51 patients (45 were immigrants) 30 were aware of their disease and had received previous antisyphilitic treatment. As a result of thorough physical and spinal fluid examinations, the reporters found that 45% of the 51 patients from Europe, North Africa, and Israel had pathological findings whereas only 26% of the Persia-Iraq group had pathological cerebrospinal fluid findings or late lesions of syphilis.

The case of an 81-year-old man, hospitalized at Saint-Brieuc with a presumptive diagnosis of "tuberculosis or sarcoidosis" is discussed by Masure and Brochen.[111] The salient features of this case were the polymorphism and multiplicity of the lesions of the skin (tertiary efflorescence), the extremely long period of latency (1893-1956), the remarkable general well-being, the integrity of the nervous system, and the normal behavior. The good health of his descendants, the absence of cardiovascular involvement except for aneurysm of the brachiocephalic arterial trunk that was discovered by chance on a roentgenogram, and the remarkable effectiveness of penicillin therapy resulting in considerable improvement in the patient's vision are also surprising features of this case.

Syphilis and Cancer.—Grosse [112] studied the problem of a possible relationship between syphilis and malignant tumors on the basis of autopsy findings. Syphilis and syphilis therapy hardly influences the predisposition to tumor formation but local predisposition seems to be slightly subject to their influence.

Syphilis of Bone in the Adult.—In an excellently illustrated but brief review of syphilis of the bone in the adult, Ehrenpreis [113] concludes: that

The outstanding roentgenographic diagnostic features of bone syphilis are: 1. Multiple diffuse periostitis. 2. Osteoporosis associated with areas of sclerosis. 3. So-called lacework of bone reaction which, however, may be present in certain cases of chronic, nonspecific osteomyelitis but becomes more characteristic with osteoporosis, as described. 4. Special predilection for the clavicle. 5. Sclerosis of the bones of the skull.

Rheumatoid, Gummatous, Tertiary Syphilis.—Ugazio and Barcia [114] described the case of a 62-year-old woman with rheumatoid, cutaneous gummas, and osseous lesions of syphilis. The lesions responded to penicillin therapy.

Calculus in the Epididymis Following Bilateral Syphilitic Orchitis.—Lees [115] reports on a patient with congenital syphilis with bilateral syphilitic orchitis which led to testicular atrophy and was complicated years after treatment by calculus formation in one epididymis. The patient had mild signs of eunuchoidism.

Paroxysmal Cold Hemoglobinuria.—A case of paroxysmal cold hemoglobinuria without a familial or personal history of syphilis is reported from the Dr. M. Stojanovie Hospital, Zagreb, Yugoslavia, by Milic.[116] All clinical evidence of syphilis is lacking, yet serologic tests for syphilis were strongly reactive and the TPI test was reactive to a titer of 1:80. Serologic tests were repeated 10 times and the TPI test 3 times. Despite treatment with penicillin and cortisone, the patient's condition remained unchanged. Hemolytic attacks continue with repeated reactive Donath-Landsteiner tests. The cause of this case is believed to be syphilis.

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(To be concluded)

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Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

An Outline of the Use of Iodine in Endemic Goiter

HENRY N. WAGNER Jr., M.D., Baltimore

In 1924, seventeen years after his first experiments on the pathogenesis of goiter, David Marine wrote [1]:

"Simple goiter is the easiest and cheapest of all known diseases to prevent and its control may be accomplished by available methods as soon as organized society determines to make the effort."

Thirty years later, he was forced to conclude a résumé of his investigations as follows [2]:

"We have not achieved the degree of control of simple goiter and its serious consequences (cretinism and deaf-mutism) in man that it would be reasonable to expect from past experiences and our present knowledge of thyroid physiology and chemistry. In only one country (Switzerland) is goiter prophylaxis carried out in a manner that shows every promise of its ultimate eradication."

The truth of this statement is borne out by Kelly and Snedden's thorough survey of endemic goiter reported in the Bulletin of the World Health Organization in 1958.[3] They conclude that the total of goitrous persons in the world today is probably not far short of 200,000,000.

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This work was carried out during the period of a U. S. Public Health Service research fellowship at The British Postgraduate Medical School, Hammersmith Hospital, London.

The purpose of this communication is to trace briefly the sequence of some of the main observations and experiments that have led to the present understanding of the pathogenesis of endemic goiter. Rarely is the natural history of the development of ideas in medicine better illustrated than in the unfolding of this knowledge.

In the first century A.D., Pliny the Elder stated that drinking water was a cause of goiter.

"Only men and swine are subject to swellings in the throat, which are mostly caused by the noxious quality of the water they drink."

Salernitan surgeons not later than the twelfth century recommended the ashes of sponges and seaweed for the treatment of goiter as evinces from the so-called "Bamberg Surgery" [4] where we read:

"A collection occurs in the throat which is called bozum which we are well able to cure: Rx. Asparagus, bruscus (Ruscus aculeatus), cyclamen, polypodium, viticella root, cucumber, wild cucumber, aristolochia rotunda, yarrow root, seaweed, marine sponge, branca ursina, saponaria, the milk of a sow nursing her first litter, and roots of thapsia. Prepare as follows: Dry all the ingredients in the sun or in the oven, then grind and sift them, then burn the seaweed and the sponge and mix it with the foregoing to make an electuary. When the patient retires, put it under his tongue."

Detail of a painting, "The Flagellation of Christ," by Hans Holbein, in 1515.

Somewhat later, Arnold of Villanova (1235-1311) and Valescus of Taranta (1418) suggested a preparation containing these same ingredients. In 1280, Marco Polo wrote:

"The people (of Yarcan) . . . have plenty of everything (particularly of cotton. The inhabitants are also great craftsmen, but a large portion of them have swollen legs, and great crops at the throat, which arises from some quality of their drinking water.)." [5]

In 1527, Paracelsus stated in lectures to his students that drinking water was a cause of goiter.[6] He alluded to iron sulfide as the responsible substance.

Thus, the idea that goiter was a disease resulting from something in the drinking water prevailed for centuries. Concurrently, goiter was being treated by administering various marine products. It was not learned until centuries later that iodine was the agent in these substances that was important in thyroid pathophysiology.

The first milestone along the road to the modern understanding of the role of iodine in thyroid physiology occurred when Courtois,* a saltpeter manufacturer in France, called the attention of a chemist named Clement to a new gas that he had discovered. Significantly, it was wartime research that resulted in both the discovery of iodine (1809) and the development of the important diagnostic and therapeutic weapon, radioiodine (1942). Significantly also perhaps was the fact that controversy involving iodine began with its discovery and has continued to the present time. Desormes and Clement announced Courtois' discovery at the Institute Imperial de France in 1813.[8] Two months later, the following was recorded in the Proceedings of the Royal Society in London [9]:

"Sir Humphrey Davy communicated, in a letter to the President, a long paper from Paris, on a new gas discovered in that city by M. Courtois, a manufacturer of saltpeter. It appears that this gas was discovered about two years ago, but such is the deplorable state of scientific men in France that no account of it was published till the arrival of our English philosopher there . . . M. Gay-Lussac has devoted his attention to an examination of its history and properties. Mean time, Sir Humphrey has made a great number of experiments on it, and would have made several more had he not wanted the necessary apparatus in Paris."

This apparently was the beginning of a dispute between Davy and Gay-Lussac that lasted for years. Chattaway writes [8]:

"Courtois discovered iodine and prepared it in a pure state; Gay-Lussac thoroughly investigated it, demonstrated its close relationship to chlorine, established its elementary nature and named it. Davy did little more than make these discoveries known in England."

* The discovery was first announced in the newspaper *Le Moniteur Universal*, No. 336, Dec. 2, 1813, p. 1344, Col. 1. Later reported in *Annales de chimie* 88:304, 1813.

On the other hand, Sharp states [10]:

"Both Courtois and Clement failed to recognize that iodine was an element; this honour being reserved for Davy who gave it its name. Gay-Lussac laid claim to the title of this discovery and he certainly was the first—in 1813—actually to publish the fact that iodine was an element, but it appears that Davy had communicated the fact to Gay-Lussac during a conversation which took place between the two men while Davy was on a visit to Paris. Altogether the weight of evidence as to priority of discovery is in favor of Davy, but he failed to get it into print first."

The relationship between iodine and goiter was suggested by Coindet, who reported the discovery of a "remedy against goiter." [7] Only eight years after the discovery of iodine, he guessed that the substance in burned sponge that had been found to be effective in goiter for at least seven centuries was iodine. Fyfe, an Edinburgh chemist, had reported in 1819 "some experiments made with a view of ascertaining the different substances from which iodine can be procured." [11] He found high concentrations of iodine in marine products, including sponge. He also concluded, however, that iodine was confined to the vegetable world. A description of Coindet's discovery appears in an anonymous article in the *Edinburgh Medical and Surgical Journal* of 1824:

"We learn from the first memoir of Dr. Coindet, that in the year 1813, when searching for a formula in the work of Cadet, he found that Russell had recommended the ashes of *fucus vesiculosus*, or bladderwrack, under the name of A. vegetabilis, for the cure of bronchocele †; and he was led, from analogy between this substance and burnt sponge, so long famed, to suspect that iodine was the active principle of both. The great and unequaled success which resulted from its use, in the treatment of bronchocele, at once indicated the power of iodine as a therapeutic agent, and encouraged Dr. Coindet to pursue his researches in rendering it an efficient article in the materia medica. . . .

"It is in medicine, as in other practical applications of human knowledge,—that few innovations entitled to the name of discovery,—few changes distinguished for sagacious conjecture, can be effected, without giving rise to dispute about the merits of the individual with whom the improvement was supposed to originate. It has been generally understood among the profession that the happy conjecture, which introduced iodine into medical treatment, originated with Dr. Coindet of Geneva; yet we find that his claim to his honour is disputed by one of his countrymen, Dr. J. C. Straub of Hofwyl, in the Canton of Berne. It is always difficult, and sometimes unsafe, to attempt to decide a question of this sort." [12]

After several years during which iodine was used in the treatment of endemic goiter, the idea was presented that it was the lack of something, rather than the presence of something, in drinking water that caused goiter. In 1830, Prévost, a Swiss, stated that iodine deficiency might be responsible for goiter.[13] The following year, Boussingault, a French chemist, recommended that domestic salt supplies should be iodized to prevent goiter.[14] The circumstances of this recommendation are described by Kelly and Snedden:

"In 1824 von Humboldt described the occurrence of goiter in the Andean plateau and referred to the striking fact that the inhabitants of goitrous localities recognized that salt from certain natural deposits was more beneficial than that from others. The following year, a young doctor named Roulin, who had recently come to Columbia from Paris full of information and ideas about Coindet's new iodine treatment of goiter, noted this and was instrumental in having samples of the salts analyzed by Boussingault. On analysis, Boussingault made the significant discovery that those salts instinctively preferred by the goitrous peoples contained most iodine. This prompted his recommendation." [8]

† In older literature, the term bronchocele was used for goiter.

In 1852, Chatin, a Professor of Pharmacy in Paris, published a long series of papers on the natural occurrence of iodine.[15] He demonstrated a lack of iodine in the air, soil, and water in districts of endemic goiter and recommended iodinization of the water supply. His experiments were severely criticized on technical grounds by a commission of the French Academy of Science, and his recommendations ignored. Meanwhile, Boussingault's recommendation had resulted in the experimental use of iodized salt in several French districts. Large doses of iodine were given in the form of iodized salt, potassium iodide tablets and by inhalation. These measures resulted in toxic symptoms, and the studies were abandoned.

Over 50 years were to elapse before further studies of the use of iodine in the prophylaxis of endemic goiter were made. The renewed emphasis on iodine resulted from the work of Baumann, who in 1896, showed that the human thyroid contained iodine.[16] Shortly afterward, Marine carried out his classic experiments. We are fortunate to have a description by Marine of the evolution of his experiments:

"My first visit to Michigan was in March, 1907, when I made a horse-and-buggy visit to several farms between Ann Arbor and Pontiac to get a first-hand acquaintance with endemic goiter in sheep and to add to our collection of thyroids of cretin and goitrous dogs and calves the thyroids of cretin lambs which were at that time not easily obtained in northern Ohio. . . .

"The iodine content of a large series of dog, pig, cattle and also fish thyroids was found generally to vary inversely with the degree of hyperplasia. . . .

"When we tried to correlate these comparatively simple relations in animal thyroids with the morphology and iodine contents of series of human thyroids, both autopsy and surgical, we encountered difficulties. . . . Most of the so-called colloid and nodular goiters were too variable in morphology and iodine content to be correlated with the animal series.

"On June 5, 1907, Lenhart and I removed one lobe (of the thyroid of an 11 year old dog.) . . . which we classified as 'colloid goiter.' "

Forty-six days later they removed half of the remaining lobe and again the appearance was that of colloid goiter. However, when they later removed portions of the remaining bit of thyroid, they found moderate hyperplasia and then, still later, marked hyperplasia.

"These and similar experiments established in our minds that compensatory hyperplasia in these long-standing and morphologically highly complex goiters was essentially identical with that observed by Halsted for normal thyroids of dogs. I think it was the most satisfying group of experiments we ever did. We now had a clue." [2] They thus came to regard goiter as an exaggeration of the normal physiological processes of hyperplasia with iodine deficiency and involution with iodine excess.

These studies provided the impetus to widespread use of iodine in an attempt to prevent goiter. Soon after Marine's work was published, O. P. Kimball carried out an experiment on goiter prevention in 10,000 school girls in Akron, Ohio, beginning in 1916.[17] Not only did the administration of iodine prevent the development of goiters, but was associated with the disappearance of thyroid enlargement in two-thirds of the girls who had thyroid enlargement at the start of the study, far more than in the untreated control patients. Elsewhere in the U. S. A. and throughout the world, Public Health Services began similar prophylactic programs. Two years later, despite many objections by physicians who were convinced that an epidemic of hyperthyroidism would be precipitated, the general use of iodized salt was begun in Michigan. By 1950, the incidence of goiter in Michigan decreased to 1% as compared to 38.6% in 1924. In 1948, the Endemic Goiter Committee of the American Public Health Association felt that endemic goiter should be classified as a deficiency disease and that federal legislation should be introduced to carry out goiter

prophylaxis by the continuous use of iodized salt. This proposal failed to pass in the U. S., but similar legislation was finally enacted in Canada and Columbia.[17]

What then is the present status of the use of iodine in the prophylaxis of endemic goiter? On the one hand, there are those, such as Greenwald,[18] who believe that iodine prophylaxis of goiter is unnecessary. He presents evidence that goiter was diminishing in prevalence and intensity in Switzerland for more than 50 years before iodized salt was introduced. Similar changes have been reported from England and other countries. Greenwald has drawn the analogy that iodinization of salt in an effort to prevent goiter is like "emptying the ocean with a pail when the tide is running out."

On the other hand, proponents of iodinization point to the tremendous body of data supporting iodinization as a useful prophylactic measure. They maintain that the harmful effects of iodinization, properly carried out, are negligible. Furthermore, these investigators have not maintained that lack of iodine is the sole cause of goiter.

Fortunately, the problem is under active investigation at present. Recent studies, such as those of Stanbury, Roche, Pitt-Rivers and others, have contributed to our understanding of the more detailed intermediary metabolism of the thyroid gland. Consequently, we may soon be able to have further evidence on some of the important questions that are now unanswered.

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Contributions of Basic Science to Modern Medicine

The papers which follow are the first of a series of four on renal physiology. Dr. Charles S. Davidson, who has assumed special responsibility for this section of the ARCHIVES, *was assisted in planning this valuable series by Dr. Maurice B. Strauss. We are deeply grateful to Dr. Strauss for his help in this regard, as well as for his own contribution which leads off the series.*

*Papers No. 3, "Mechanisms of Urinary Concentration and Dilution," by Dr. Ezra Lamdin, and No. 4, "Renal Excretion of Calcium and Phosphorus" by Dr. David D. Thompson, will appear in the April and May issues, respectively.**

P. S. R.

The Urine Remains the Same

Current and Countercurrent Concepts in Renal Physiology

MAURICE B. STRAUSS, M.D., Boston

The following letter of transmission accompanied Dr. Strauss' article. Hoping our readers will find in it a hearty chuckle, as we did, we share it with you.

P. S. R.

"I am enclosing my introduction for the three papers on renal physiology. The title derives from a Greek inscription which possibly may be construed to mean 'old urine in new kidneys.' When the Permian Puddingstone rock formation was being excavated for the foundation of our hospital this inscription was found on a sheet of membranous material, faintly ruled in semilogarithmic fashion, which was unearthed. The membrane, while being prepared for C^{14} analysis to determine its age was unfortunately burnt to an ash, analysis of which is consistent with the hypothesis that the membrane had once been saturated with late Paleozoic urine.

M. B. S."

Although the history of renal physiology may be said to begin with Ludwig a little over a century ago, the external secretion of the kidney—urine—has commanded man's interest for several millennia, in fact, virtually as far back as the written record goes. Sumerian, Babylonian, and Hindu physicians examined the urine for diagnostic and prognostic purposes. Hippocratic texts are said to describe the character of the urine in disease 182 times.[1] Thus, it can scarcely be doubted that examination of the urine was the forebear of all the multitudinous laboratory examinations which are now practiced on all readily available (and some rather inaccessible) materials which can be removed from the body of man. Actually, urinalysis was almost the only laboratory procedure in common use until the twentieth century. Volumes as thick as those that now embrace the whole of quantitative clinical chemistry were devoted almost exclusively to the examination of the urine. A book entitled "Kidney Diseases, Urinary Deposits, and Calculous Disorders," first published in 1861, allots 89 pages to the kidney and its diseases, 85 pages to the analysis of healthy urine, and 250 pages to the examination of the urine in disease.[2]

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* Because of the large number of requests anticipated for reprints of the papers of this series, it is planned to bind them together after the last has appeared. They may be obtained by addressing requests to Mr. Edward T. McNabb, Baird-Ward Printing Company, Box 539, Nashville 1, Tenn.

Many inorganic salts, including those of ammonium, sodium, calcium, magnesium, and potassium, now prepared more profitably from other sources, were originally isolated from urine by the early alchemists and later chemists. Pure phosphorus was first obtained from this source in 1669. A hundred years later Von Rouelle extracted the residue of evaporated human urine with alcohol and obtained urea for the first time. It is noteworthy that some 55 years later, in 1828, Wöhler prepared urea "artificially" from ammonium cyanate—the first "organic" substances to be prepared by man. The impact of this event may be difficult for us to appreciate in the present era of exceedingly complex organic syntheses, but until Wöhler's landmark, the in vitro preparation of organic materials was considered impossible.

Urine, both fresh and in the decomposed state, in addition to being a source of many materials useful in the arts and crafts, was endowed with many therapeutic properties and was employed internally and externally for a variety of purposes. The kidney, too, has been invested with mysterious powers. At one time, it was thought capable of reabsorbing an "ideal" fluid from the glomerular filtrate; recently, it was credited with producing the manifestations of chronic congestive heart failure; today, it is being studied as a prime mover in both polycythemia and anemia.

A few decades ago each kidney in man consisted of approximately one million essentially identical excretory units—the nephrons—emptying into a far smaller number of collecting tubules and thence by way of the papillary ducts into the renal calyces. Each glomerulus received a relatively fixed supply of arterial blood of constant composition and filtered off about 20% of the water and diffusible solutes from the plasma. To be sure, only one of eight nephrons possessed a long thin limb and anatomic dissection of nephrons had most thoroughly demonstrated inhomogeneity. Nevertheless, it was comforting to believe that one glomerulus was much like another, and that there was no important difference between long and short tubules.

The development of modern clearance techniques (foreshadowed in the work of Van Slyke and Rehberg) by Dr. Homer Smith and his associates facilitated viewing the kidney as a uniform collection of identical nephrons. The constancy, in man, of inulin clearance (considered a measure of glomerular filtration rate), of diodrast and para-aminohippurate clearances (considered measures of effective renal plasma flow), of calculated tubular maximal rates of secretion and reabsorption for a number of substances all seemed to favor such a simplifying concept. The diagrammatic representation of the nephron as a straight tubule connected to a glomerulus, although indicating linear differences between proximal, distal, and thin limb, necessarily neglected the curious architectural pattern produced by the thin limb and its accompanying vasa recta extending almost to the tip of the papilla. The fact that only such vertebrates as possessed thin limbs were capable of concentrating the urine led to the hypothesis that the thin limb was the site of concentration. This concept was soon abandoned because such flat epithelium seemed incapable of performing osmotic work—despite clear evidence that in other anatomic areas such a flat epithelium can accomplish this task.

Today, however, we can no longer view the kidney as if it consisted of a million identical units. The work of Pappenheimer and his colleagues so ably discussed by Dr. Winton in the next paper in this series most certainly suggests that the composition of the blood perfusing each glomerulus is by no means the same as that perfusing every other one. Furthermore, if the osmotic concentration of human kidney tissue and interstitial fluid exhibits a gradient from a cortical osmolality of 300 mOsm. to one of 1,200 or more at the tip of the papillae, as discussed in Dr. Lamdin's paper, then nephrons with long loops of Henle must be entirely different from those without such

extensions, and flat epithelium may not be dismissed lightly.

The past decade has seen other comfortable simplifications vanish in the light of new investigation. The urine a few years ago was acidified by the simple process of reabsorbing the filtered disodium phosphate and allowing the monosodium form to be excreted. Now, the tubules are the seat of complex ion exchanges and the reabsorption of bicarbonate is accomplished by mechanisms probably subject to the laws of enzyme kinetics.[3] Urea, filtered at the glomerulus, formerly diffused back through the tubular epithelium to an extent determined only by the rate of luminal flow. Today, it is strongly suggested that urea is subject to active transport and cannot be considered as an inert substance excreted or retained by purely physical forces.[4] Urinary potassium, until recently, had never been found to exceed filtered potassium. Thus, it was assumed that the potassium found in the urine was the unreabsorbed residue of that filtered. Today, the thesis advanced is that virtually all the filtered potassium is reabsorbed and that the urinary potassium is subsequently secreted by the tubular cells.

One may well inquire why these earlier concepts came to be so universally accepted and why they are now so rudely rejected. In this connection it appears worth while to review a few historic aspects. Although Ludwig in 1844, shortly after Bowman's detailed description of the Malpighian corpuscle, presented the view that urine production began with the formation of a protein-free ultrafiltrate of plasma, this was not verified by actual analysis until 1923, when the work of Richards, Wearn, Walker, and their associates commenced. However gratifying was this demonstration, it did not become maximally useful in the study of the intact animal until Shannon and Smith in 1935 established that the clearance of inulin constituted a reasonably good index of the rate of glomerular filtration.[5] The investigator then had well-defined parameters—the rate of formation and the composition of glomerular filtrate, together with the rate of excretion and the ultimate composition of the urine. Obviously, whatever differences existed between these two fluids were the result of phenomena occurring within the renal tubules. Walker, Bott, Oliver, and MacDowell[6] succeeded in puncturing and obtaining luminal fluid from a sufficient number of mammalian proximal tubules to make it clear that the volume of filtrate was progressively reduced by at least two-thirds in this segment without change in its osmolality. They demonstrated the virtually complete reabsorption of glucose in the proximal tubule, as well as an increase in chloride concentration such as to suggest the complete replacement of bicarbonate. Since Walker and his associates were able to secure luminal fluid only three times from mammalian distal tubules, further physiological dissection of the renal tubule had to be accomplished by the drawing of inferences based on two measurements—glomerular filtrate and ultimate urine—and the acceptance of a variety of assumptions. As one reviews the latter it becomes apparent that at first they were advanced as hypotheses and the original workers never considered them to be more than such. Then, adverse evidence not being forthcoming, they came to be accepted as verities despite the absence of further confirmatory evidence. It thus becomes incumbent upon the investigator of renal physiology to scrutinize his reasoning so as not to lose sight of the fact that certain of his basic assumptions may represent nothing more than unproved hypotheses. For example, the Fick principle obviously can only be applied to the measurement of renal plasma flow if the arteriovenous difference in concentration of the test substance is known. Although a constant difference may be found in certain studies, application to other studies is unwarranted. Homer Smith in his monumental monograph on the kidney[7] pointed out the many pitfalls involved in the use of *p*-aminohippurate (PAH) and allied clearances as indices of renal plasma and blood flow. Clearly, he outlined the fact that the very

act of injection of certain of the commercially available preparations could have significant hemodynamic effects; that the extent of penetration of the material into red cells and the degree of release or further penetration between arterial and renal venous blood could not be overlooked; that the analysis of "renal venous" blood from the left renal vein was prone to give erroneous extraction ratios because of admixture of nonrenal venous blood—and that right renal vein blood was not invariably beyond suspicion; that obviously a "standard" plasma extraction ratio could not be applied to all sorts of subjects and situations. Recently Sellwood and Verney [8] compared the values for renal plasma flow determined by direct measurement of blood flow and hematocrit with those obtained by the application of the Fick principle. Underestimation by as much as 30% was observed even when the PAH content of renal arterial and venous blood plasma was determined analytically. The assumption, then, that PAH clearance, based on a standard extraction ratio, is a valid measure of renal plasma flow must be viewed as unwarranted. Probably one is justified in concluding that when such a calculated PAH clearance remains constant during the course of numerous successive experimental periods, it reflects a relative stability in renal plasma flow although it does not indicate its precise magnitude. Marked changes in PAH clearance when not rapidly fluctuating and not correlated directly with urine flow probably reflect changes in renal plasma flow, but again do not necessarily indicate their true magnitude.

Similarly, limitations, if less rigid, must also be applied to inulin clearance, although obviously extraction ratios are not involved. However, even with relatively constant rates of urine flow, changes of 10% or more are frequently encountered during continuous observation periods. Need for precaution in interpretation has been recorded by the originators of the clearance techniques: "Absolute values of renal clearances are not highly significant except when they are the average of several consecutive periods . . . and even in the same individual the average clearances must be interpreted with caution pertinent to the interpretation of biostatistical data of any kind." [9] Unfortunately, such caution has not always been observed by subsequent investigators.

A new technique, the stop-flow analysis of tubular function, is now coming into increased use. Since it employs the condition of osmotic diuresis, a word of caution needs to be introduced. In most terrestrial mammals thirst is such an efficient regulator of water intake that diuresis of any type is an unusual occurrence and the volume of urine is seldom more than 1% of the glomerular filtrate. The anatomy of the kidney, with the coalescence of many tubules into a smaller and smaller number of collecting ducts, is well adapted to this state. When, however, either in water diuresis or osmotic diuresis more than 10% of the glomerular filtrate issues from the collecting ducts, the normal situation is markedly altered. Gottschalk and Mylle [10] have shown that in the latter type of diuresis the normal pressure differential between proximal and distal tubules is virtually abolished, as both systems become dilated and intratubular pressure rises to several times control levels. Concomitantly peritubular capillary pressure is also elevated.

Dr. Thompson's review of the renal excretion of calcium and phosphorus which concludes this series concerns an area in which the investigator's problems are far from simple. With calcium in the serum existing in bound, complexed, and ionized forms, the difficulty of ascertaining even the first parameter of the renal physiologist—the filtered load—is apparent. Nevertheless, increasing awareness that hyperparathyroidism is not as rare a disorder as once thought [11,12] has led to a search for means of identifying the doubtful cases of this condition, particularly when, as is so common, there are only renal manifestations and no skeletal abnormalities. Hypercalcemia and hypophosphatemia need not be marked. The renal impairment caused by the disease

may cause the disappearance of hypercalciuria and elevate serum phosphorus to, or above, normal values. Since the phosphaturic action of parathyroid extract [18] is manifest despite a lowered serum phosphate level (and a lowered filtered load of phosphate), numerous attempts have been made to devise a procedure, based on the tubular handling of a usual or increased phosphate load, which would identify patients with primary parathyroid disease. Unfortunately, all such tests seem admirably fitted to differentiate between the obviously normal and the patently hyperparathyroid subject. They fail to identify which of the patients in whom the diagnosis is questionable (and where the physician most needs positive assurance) requires dissection of the neck and even of the mediastinum.

Conclusion

The renal physiologist must perforce turn to the laboratory animal for much of his research. The dog is admirably suited, both by size and temperament, for many investigations. Yet it must be noted that there are rather marked differences between the carnivorous, quadripedal canine and the omnivorous, bipedal human. The former's ancestors are presumed to have hunted until achieving a kill and then to have gorged to satiety, thereby presenting their excretory mechanisms with a large load of nitrogen and a surplus of sodium (the latter derived from the extracellular fluid of their prey). The canine's filtration rate changes rapidly in response to changes in diet and salt intake. The ancestors of man, if they resembled present day anthropoids, were largely herbivorous, subsisting on nuts and fruits, grains, leaves and shoots, and spent five or six hours daily in feeding, thus hardly ever ingesting more than a minimum of sodium and generally presenting a relatively constant load of nitrogen for excretion. Man's filtration rate is remarkably stable.

The history of renal physiology has passed through many periods, each dependent on the currently available techniques: for centuries there was only analysis of the urine; then came anatomic dissection of the kidney coupled with brilliant speculation; micropuncture techniques afforded the first solid factual basis for current concepts, but were soon succeeded by the less exacting procedures of chemical clearance and interpretive dissection; micropuncture analysis, relatively little employed for a decade, is now again supplying solid facts.

The renal physiologist has often coupled a superb imagination with the techniques of his day. There is no reason to believe that this will cease, but, rather, with improved techniques one may anticipate even greater flights of speculative imagination.

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Present Concepts of the Renal Circulation

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Thirty years ago physiologists' ideas about blood circulation in the kidney were based on what was known of its structure. The branching arterial system supplied the glomerular capillaries, which recombined to form efferent arterioles which fed a second capillary system around the tubules. Accordingly, the glomerular capillary pressure would be higher and the peritubular capillary pressure lower than pressures in the capillaries elsewhere in the body, with consequent pressing out of ultrafiltrate in the glomeruli and the sucking back from the tubules of most of it by colloid osmotic action of plasma proteins.

Then methods of measuring blood flow were developed, including direct measurements in isolated perfused kidneys, flowmeters in anesthetized animals and later the indirect clearance methods which can be used in unanesthetized animals and man. Experiments spoiled the simple and satisfying theory. The blood flow did not increase proportionately or more than proportionately with pressure as it does in other organs. Glomerular filtration rate did not respond to pressure change as do normal filtration processes. Arteriovenous shunts of various kinds were revealed by angiographs and injection procedures. Intermittent glomerular activity seen in the frog and suspected, though not yet confirmed, in mammals implied the contribution of only some probably variable fraction of nephrons to the circulation. Arteriovenous oxygen difference was low and independent of blood flow in the kidney, whereas it varies inversely as the blood flow in other organs, so as to keep the oxygen consumption fairly steady.

These are some of the major clues to current ideas about renal circulation which have been developing more and more rapidly in recent years. Different theories are now put forward by different physiologists as the simplest explanations of the experimental facts. It may well be that each of these is too simple to account for all the facts and that two or more of the theories will have to be combined. This has happened before in renal physiology when the "filtration-reabsorption theory" so relentlessly advocated in comparatively recent times by A. R. Cushny and A. N. Richards had eventually to be combined with its rival "secretion theory" in a form in which it now commands general acceptance.

The Intrarenal Circulatory Apparatus

We have known for a long time [1] that the blood flow through the kidney is much less increased by rise in arterial pressure than might be expected. This only holds within a range of pressure about 70 mm. to 200 mm. Hg, and since it is known to be an intrinsic property of the kidney, not due to nervous or hormonal control from outside, it is termed autoregulation. By contrast, a change in the arteriovenous pressure head produced solely by change in venous pressure is not governed by autoregulation, and produces in acute experiments a change in flow about proportional to the change in pressure.[2]

Autoregulation implies an increasing renal resistance, i. e., pressure divided by

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flow, with increasing arterial pressure. In any system the over-all resistance to flow may be varied either by change in the sizes of the tubes or by change in the viscosity of the liquid. At the moment there are two challenging theories of autoregulation based on these alternatives. The view most widely held attributes the increase in resistance to vasoconstriction of renal blood vessels, but this fails to explain several other physiological properties of the kidney. Consequently, a theory based on a change of resistance due to a change in the effective viscosity of blood within the renal vessels has been put forward, and this explains those other curious properties of the kidney rather well, but again it falls short of explaining all the known experimental observations. Perhaps both theories are right, and each plays its part in varying degrees in maintaining autoregulation. Autoregulation is a sensitive affair, easily impaired by experimental disturbance of the kidney, and probably also by disease. It is well, therefore, to survey some of the properties of the kidney which these theories seem to illuminate.

The facts to be explained by the *vasoconstrictor theory* may be summarized, roughly following Waugh,[3] by saying that a 50% rise in arterial pressure will produce about a 3%-5% rise in renal blood flow in the unanesthetized rabbit[4] or dog[5]; an 8% rise in a kidney perfused from an anesthetized dog, although the hematocrit has been reduced to about 15%[3]; a 20% rise in a dog kidney perfused with defibrinated blood from a pump-lung preparation[6]; a 22% rise when perfused with dextran solution with or without oxygen,[3] but after arrest of flow for 4 to 10 minutes the kidney has deteriorated so that with dextran perfusion there is now a 34% rise. With the pump-lung kidney preparation and the blood cooled to 3-12 C there is a 35% rise.[6] Drugs like cyanide[7,8] and procaine can abolish autoregulation, procaine dextran solution giving a rise of 59%[3]; on the other hand, chloral hydrate in plain muscle-paralyzing concentration impairs but does not abolish autoregulation.[6] Oxygenated light oil perfusion gives a rise of 69%.[3] With blood perfusion a glass tube would give a rise in flow of 50% and a perfused dog hind-limb about 60%.[9]

Many but not all of these observations fit well into the vasoconstrictor theory. For example, poisoning the plain muscle in the arterioles with cyanide or procaine abolishes autoregulation, as might be expected. On the other hand, chloral hydrate which also abolishes the responsiveness of plain muscle only impairs autoregulation. These drugs, like cold, produce a rise in intrarenal pressure which impedes the venous outflow of blood equally at all arterial pressures.[6] If blood is cooled, therefore, the intrarenal pressure accounts for a substantially larger fraction of the arteriovenous pressure fall at low than at high arterial pressures. If the viscosity of blood is doubled, judged by the resistance in a glass tube, by cooling it to 11 C, the resistance of a dog kidney, in excess of that due to intrarenal pressure, is also doubled compared with that at 37 C; this is so at arterial pressures from 70 mm. to 160 mm. In this sense autoregulation is quite as good at 11 C as at 37 C.[10] Oxygen lack does not impair autoregulation, but this does not prevent vasoconstriction, since plain muscle is not immediately dependent on oxygen supply. Most perfusion media, including plasma, pass to an unknown but probably very large extent across capillary walls into the tissue spaces, thence to the lymph or back into the bloodstream. Oil and kerosene are confined to the vascular system, but autoregulation is unfortunately abolished in kidneys perfused by them.

Some of these observations support the vasoconstrictor theory indirectly, only by seeming to disprove the alternative theory of viscosity changes in blood due to change in the hematocrit in some renal blood vessels. The latter theory could not explain why perfusion with fluids like dextran, without cells, shows some degree of autoregulation, at least in these dextran-perfused dog kidneys.[3] Moreover, anesthetized dogs in which the hematocrit has been greatly re-

duced still show good autoregulation.[3,11] On the other hand autoregulation in the cat kidney usually vanishes when cells are absent from the fluid [12] and is progressively impaired as the hematocrit of the blood is reduced.

The above facts, therefore, support the vasoconstrictor theory by showing that some poisons abolish autoregulation. Since nobody has yet thought of a plausible theory of autoregulation, other than the vasoconstrictor and the viscosity theories, which has not been disproved, evidence that autoregulation exists in the absence of viscosity change, i. e., during perfusion with cell-free media as it does in the dog, can be taken as strong support for the contribution of vasoconstriction to autoregulation. It does not, of course, sustain a contention that viscosity changes do not contribute to autoregulation in normal animals, and we may now turn to experiments which support the viscosity theory and cannot easily be interpreted in terms of the vasoconstrictor theory.

In normal liquids flowing smoothly in glass tubes the flow is proportional to the pressure, as found by Poiseuille, in 1843, in connection with his work on the blood circulation rate in the horse. For a given tube, the resistance to flow depends on the nature of the liquid and on its temperature but not on the velocity of flow, short of turbulence. If a viscid liquid exhibits, say fivefold the resistance of water in one tube, it will still be fivefold in another tube with a much smaller bore, even if the absolute resistances have increased one-hundred-fold. This is not true of a heterogenous liquid like blood, because when it flows the cells concentrate down the center of a small tube leaving the liquid near the walls comparatively cell-free and much less viscid than whole blood. But it is in this cell-free zone that most of the movement of the liquid takes place relative to the stationary layer next to the wall of the tube. Consequently, whereas blood may be four or five times as viscid as water in tubes of 1 mm. bore, it falls to not much more than one-half of this in tubes of diameter about the same as that of arterioles which provide the main resistance in the vascular system. In a dog hindlimb perfused with blood or Ringer's solution the ratio of the flows, at equal pressures, will be about 2.5, whereas the same liquids flowing through a large glass tube will show a ratio of five at the same temperature.[9] In a system in which smaller vessels branch off a comparatively larger vessel, the cell-free plasma in the outer zone of the main vessel passes into the branches, whereas most of the cells pass on in the main vessel. This cell-separation was called plasma-skimming by Krogh [13] and is seen microscopically in many tissues including the human retina.[14]

The *cell-separation theory* of Pappenheimer and Kinter [15] in its simplest form explains autoregulation in the kidney by supposing that the cell-poor plasma, so fed to the vasa afferentia from the interlobular arteries, passes through the glomerular-peritubular capillary system and that the cell-rich fraction of the blood that remains in the interlobular arteries passes through shunts. The axial movement of the cells depends on the movement of blood along the tube and derives its energy from the arterial pressure. It is natural to suppose, therefore, that increased arterial pressure will increase the degree of cell separation. In this way polycythemic blood with corpuscular concentration of maybe 80% or so may be produced and is believed to pass through the shunts. It is only in such high concentrations of cells that the viscosity varies greatly with small changes in cell content.[9] At normal hematocrits the viscosity rises comparatively little with rise in cell concentration. That is why the rise in the blood left behind after glomerular filtration is too small to be significant in this connection.[6]

What observations on the kidney can best be described by the cell-separation theory? First, the low dynamic hematocrit of the blood in the renal vessels has been established in many laboratories and by many different direct methods.[15-17] At normal blood flows the intrarenal hematocrit may

be less than half of that in the arterial or venous blood. It is not easy to explain this without cell separation, the cell-rich fraction in the shunts occupying a smaller volume than the cell-poor fraction in the glomerulotubular capillaries. If this is so, the cell-rich fluid must flow correspondingly faster so as to combine with the slower moving cell-poor fluid in the veins to form blood of normal hematocrit. A unit of cells does not, however, seem to pass much more quickly from artery to vein than a unit of plasma albumin [18] and this has been taken as indirect evidence that the low intrarenal hematocrits shown by direct experiment must in some way be misleading. It is clear that both hematocrit and circulation time are likely to be widely different in different parts of the kidney and that more needs to be discovered about this. Meanwhile, it is fair to prefer the direct evidence that intrarenal hematocrit is very low, and inevitably, therefore, that there is some cell separation. Pappenheimer and Kinter [15] have shown further that the intrarenal hematocrit becomes lower at higher arterial pressures, hence, that the degree of cell separation is increased with rise in pressure which thus raises the resistance of the kidney to blood flow.

A second pointer to this theory is provided by the high extraction ratios of substances like PAH and iodopyracet (Diodrast) used to estimate renal plasma flow. It has been argued [19] that these show that all or nearly all of the blood must pass through the peritubular capillaries and hence that there can be no shunts of the kind described by Trueta et al.[20] But high extraction ratios in fact only show that the plasma passes by way of the peritubular capillaries. The red cells could well flow through shunts. Suppose that the kidney were perfused with blood with a very low hematocrit, however, there would be very few cells to occupy the shunts and to prevent some of the plasma flowing that way. The extraction ratio should, therefore, fall; and so it does,[21] despite the undiminished secretory activity, Tm_{PAH}, of the cells concerned.

There are, moreover, several unexpected features of the relative oxygen tensions in the blood and urine which point to cell separation. Arteriovenous oxygen difference is unusually low in the kidney corresponding to the unusually high blood flow for that mass of tissue. More curious is the well-established constancy of renal arteriovenous oxygen difference during changes of blood flow, in contrast with the inverse relation found in other organs which thus keep the oxygen consumption approximately constant. This property is well developed in isolated kidneys, but holds only over the range of arterial pressure within which autoregulation obtains. Below this, i. e., below about 70 mm. Hg, the usual inverse relation between blood flow and arteriovenous oxygen difference is found in the kidney as in other organs.[22] The independence within the autoregulatory range can be explained along the general lines that most of the red corpuscles pass through shunts and lose little or none of their arterial oxygen. Most of the plasma passing through the capillary system loses almost all of its oxygen at whatever rate of flow, so that when plasma and cells recombine in the venous blood the oxygen content is independent of flow.

Important additional information has recently appeared [23,24] in this connection. Anesthetized dogs were allowed to breathe oxygen at various pressures, and the relation between oxygen tensions in venous blood and pelvic urine were compared both in dogs which happen naturally to have a high diodrast extraction ratio and in dogs which have a low one. With the dogs breathing 1 atmosphere of O_2, the venous oxygen averaged 80 mm. Hg and the urine oxygen about 38 mm. in high-extraction dogs but 70 mm. in low-extraction dogs. If the urine oxygen is taken as an approximate measure of the oxygen in the peritubular capillaries it shows that the capillary content is more deoxygenated in the high-extraction kidneys. This could be due either to higher oxygen consumption in these kidneys or to less hemoglobin in the

capillary fluid. That the second is the correct explanation is indicated by further observations at higher and lower inspired oxygen concentration. In this way venous oxygen was varied from 50 mm. to 860 mm., with corresponding urine oxygen pressures of 27 mm. and 120 mm. in high-extraction kidneys. The renal oxygen consumption was unaffected, so that the change in oxygen gradient from blood to urine cannot be explained this way. The gradient of over 700 mm. at the high oxygen tensions must be taken to imply a correspondingly low level of the oxygen pressure in the peritubular capillaries. The fixed quantity of oxygen, measured as oxygen consumption, lowers the oxygen pressure in blood with a normal hemoglobin content comparatively little, but if the hemoglobin content is low, as it would be after cell-separation, much of the oxygen has to be derived from that in physical solution in the plasma, with a much larger fall in oxygen pressure for the given quantity of oxygen lost. This, therefore, again supports the cell-separation theory and indicates that the separation is less in degree in the low extraction ratio kidneys than in the high extraction ones. Very different reasons for this conclusion have already been given above.

It will be seen that there are some positive indications for the cell-separation theory: the absence of autoregulation in the absence of cells which is found in the cat, the low renal dynamic hematocrit which is lower at higher arterial pressures, the dependence of high extraction ratios of diodrast and PAH on the presence of cells in the blood, the independence of arteriovenous oxygen difference and blood flow, and the unexpectedly low oxygen pressures in urine, particularly when blood oxygen pressure is raised. The exceptionally high blood flow through the kidney per gram of tissue has itself recently been described as more like that of arteriovenous fistulae than organs with normal circulatory structure.[25]

Positive evidence for the vasoconstrictor theory is remarkably scanty. Physiologists have for long taken the reliable criterion of a vasoconstrictor action in an organ to be the combination of increased resistance, i. e., blood pressure-flow ratio, with plethysmographic reduction of volume of the organ. Only the first of these obtains in the kidney. The volume of the kidney undoubtedly increases rather than decreases with rise in arterial pressure, and although this can be explained away it constitutes a severe blemish on the proof of vasoconstriction. Some but not all poisons abolish autoregulation which, however, persists in some degree at temperatures too low for such vital responses.

Since the cell-separation mechanism will not account for the appearance of autoregulation in some circumstances, and no other likely theory has been put forward, we have to fall back on the vasoconstrictor mechanism to explain these. But the latter can, in its turn, also not account for the appearance of autoregulation in another set of circumstances or for a number of other properties of the kidney well explained by cell separation. Both mechanisms must, therefore, be supposed to contribute to autoregulation. The degree in which they do so, and in which they fail to do so under the influence of drugs and disease, remains largely to be discovered.

In the absence of cell separation in the kidney the approximate pressure of blood in glomerular capillaries can be estimated at about 70-80 mm. Hg.[26] It is not much affected by change in arterial pressure, since glomerular filtration rate is not much affected. Such vasoconstriction as is concerned in autoregulation must, therefore, reside in the preglomerular part of the renal vascular system.

In rat kidneys micropuncture reveals a pressure of about 17 mm. Hg [27] in the vasa efferentia, and this low value is believed to account for a lower pressure in peritubular capillaries,[28] with their larger capacity for water reabsorption, than in capillaries in other organs. The pressure in the arcuate veins in the dog is remarkably high, possibly 20-25 mm. Hg,[3,29] but it is not yet

clear whether this is due to obstruction by structures between the arcuate and interlobar veins or due to compression from outside the veins exerted from fluid in the tubules.

Intrarenal pressure was at one time thought to be higher than tissue pressures in other organs and to vary with arterial pressure, possibly contributing to autoregulation of blood flow. The pressure was measured by plunging hypodermic needles into the renal substance.[30,31] It is now thought, however, that this procedure only measures pressure in an artificially produced pool of blood in the torn tissue around the tip of the needle.[26] Intrarenal pressure proper is much lower [32] and seems to play no interesting part in blood circulation, except possibly as an obstruction, independent of arterial pressure, in greatly swollen kidneys.[6,26]

The *blood volume* in the kidney is strikingly high, about 24% of its total weight at normal and 19% at low arterial pressures.[15] The content of blood per gram of tissue is very different in the cortex and medulla, and it is known that this distribution is affected by vasoconstrictor drugs. Little is, however, known of the more specific effects of drugs either on the total volume of blood or on its distribution.

Extrarenal Influences on Renal Circulation

The rich *nerve supply* to the kidney plays singularly little part in its functioning in normal animals although stimulation of the nerves, like large doses of sympathomimetic amines, produces a profound reduction in blood flow and anuria. In hypotension well below the autoregulatory range, due for example to hemorrhage, the renal blood flow falls much more, proportionately, than the cardiac output [33] and the fall is greater in innervated than in denervated kidneys.[34] Such extensive hemorrhage, like nerve stimulation or a large dose of adrenalin, produces the well-known appearances in angiograms of juxtamedullary shunts.[20] It may be noted in passing that radiopaque material reveals the position of plasma, not necessarily that of the cells, and of the plasma it reveals only the quantity but not its rate of flow.

Hormonal influences on renal circulation have more interesting effects. Lesser degrees of hemorrhage or corresponding diminution of blood volume in other ways may produce cutaneous vasoconstriction without much immediate change in renal blood flow. After an hour or two, however, substantial and sometimes damaging renal vasoconstriction develops which is attributed [35] to circulating vasoconstrictor substances.

Cardiac failure is associated with a low renal blood flow. Although a rise in venous pressure reduces renal blood flow in acute experiments, the comparatively small rise found in cardiac failure does not reduce the flow in chronic experiments. A reduction in pulse pressure which is believed to play an important part in experimental hypertension does not seem to be concerned in the renal response to cardiac failure. If cardiac output falls, the renal blood flow falls disproportionately more. Even if the cardiac output rises, as in thyrotoxicosis, the renal blood flow may fall profoundly.[35] As the flow fails to be improved by high spinal anesthesia it may well be that the reduction in renal blood flow due to cardiac failure is due to hormonal influence.

Suprarenal medullary extracts produce renal vasoconstriction to an extent which depends on the dose. In small doses they are believed to have more action on the efferent than on the afferent glomerular vessels with consequent rise in filtration rate [36] even when the arterial pressure is prevented from rising.[37,38] Normally, norepinephrine raises the G. F. R. with its large rise in arterial pressure, but large doses reduce it as does almost any effective dose of epinephrine. Some observations suggest that a reduction in blood flow due to sympathomimetic amines is due to complete shutting down of some nephrons rather than to vasoconstriction uniformly in all. This is because they produce a fall in

Tm_G proportional to the fall in G. F. R.[39] It seems unlikely that sympathomimetic hormones influence renal blood flow in normal conditions, since drugs antagonizing their actions have little effect except on the reduced flow in cardiac failure.

Drugs which affect the blood volume or cardiac output produce indirect effects on renal function. Comparatively few drugs in common use have an important action on renal blood flow in normal animals and those that do often have their effect after so long a latent period that extrarenal factors must be suspected of intervening between the drug and the kidney.

Direct action of diuretics on blood flow through the kidney is confined to the purine group which immediately increase the flow even in isolated kidneys. Vasodilatation is rather transient and is followed by vasoconstriction after a fairly short time in normal and after rather a longer time in diseased kidneys.

Vasoconstrictors, such as epinephrine and norepinephrine (arterenol), produce a reduction in renal blood flow and a contraction in the plethysmographic volume of the kidney, contrasting in this way with the increased volume during the vasoconstriction associated with autoregulation when the arterial pressure is raised. The specific actions of low concentrations of these and other drugs on autoregulation have not yet been reported.

Hypotensive drugs of the ganglion-blocking class hardly affect renal blood flow unless the arterial pressure falls below the range of autoregulation. Adrenergic blocking agents also have little effect in normal animals, confirming the view that tonic sympathetic control of renal circulation plays no part in these circumstances, though it has an effect in anesthetized animals.

Most anesthetics in sufficient dose reduce renal blood flow, but light anesthesia with Pentobarbitone and chloralose has little such action. Ether and cyclopropane have about equal actions in dogs, light anesthesia reducing renal blood flow by about 32% and deep anesthesia by 63%.[35] This vasoconstriction is quickly reversible after anesthesia ceases, and it is generally held to be prevented by denervation before administration of the anesthetic, though the increased concentration of vasoconstrictor hormones during anesthesia probably has some additional action on the kidney.

Gower St. (WC1).

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

New Bottles for New Wine. By Julian Huxley. Price, $4.50. Pp. 318, with many illustrations. Harper & Brothers, 49 E. 33d St., New York 16, 1957.

The steadily increasing complexity of the modern world cannot be understood without a well-grounded comprehension of science. While a layman may understand science, the person who has not himself engaged in scientific activity as investigator or teacher rarely has a strong grasp on what science means. Are the recurring failures on the international scene caused in part by misunderstanding or lack of understanding of the many implications of the scientific age? The science of understanding man himself, because of its great complexity, has lagged behind other fields of knowledge despite the fact that hope for the future depends to such a large degree upon clearer insights into the nature of man and a wide diffusion to these insights. Wise leadership in affairs of state, both national and international, requires as absolute prerequisite an understanding of the meaning of science deeper than any political leader in our time has had. This is true the world around. While understanding is no guarantee of survival we are doomed automatically without it.

A problem in all teaching and learning is how to bridge the gap between knowledge and the application of knowledge which leads to accomplishment and sometimes to achievement. The human intellect must master a vast body of fact to make reasonable decisions of any kind. Especially men in the difficult fields of government and statecraft need many facts. Their often belated acquisition leads to intellectual indigestion so disturbing that wisdom rarely gets a chance. We react by throwing up our hands in despair. We should try more constructive programs for improving the situation. Following the same old paths inevitably will lead to the same old conflicts which now have the forbidding dimensions of total destruction and extinction of the human race.

The differences between the known and the unknown, and the distance separating the two are hardly smaller than the chasm which separates our knowledge of the world about us from useful practices which should be based on that knowledge. The brain and hand of man somehow seem at odds with his heart, or at least his heart has not kept pace in sympathetic human understanding among men. We have cerebral tachycardia and asystole of the spirit. We have set free vast powers, neutral in themselves, but containing the seeds of incomprehensible amounts of evil or of good.

How might a biological scientist redesign our lives? Along what lines might he make changes in the world as we have it before us? These are not just whimsical speculations. Though our world today cannot be intelligible without a well-grounded understanding of science, such understanding is no guarantee that a person would take enlightened views when suddenly thrust into a position of authority. Huxley's book, "New Bottles for New Wine," a collection of lectures and essays prepared for several diverse occasions, gives a brilliantly conceived and executed blueprint for more than survival, a pattern for the more abundant life of body, mind, and spirit. His theme is that modern scientific man must make them available. Exposing the secrets of the atom in all their nakedness, a monumental act of the human intellect, puts in our hand a threat to the existence of human intellect and life, indeed of all life in the planet. But not this and not all the discoveries of flight through air or through space, the instantaneous impacts of television and radio, the health-giving skills of medicine, all increasing in the years since the end of World War II—not any of these is the great intellectual feat of the age. Rather, it is the sudden widespread awareness that man's place is nature, human destiny in its grandest but still its simplest sense, not only is comprehensible to man but has got to be managed, indeed must be manipulated by man for survival and for any hope that our only remaining road to true evolutionary change may lead forward. Thus, no man is an island. We all are concerned with man and man's place in nature.

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To this theme Julian Huxley's distinguished grandfather, Thomas Huxley, made notable and luminous contributions in the stormy climate of Victorian bewilderment after Darwinian evolution sprang as a mature concept from the mind of its inventor. A fact which the layman overlooks, and we are all laymen in most fields, is that this new vision of man and his just place in the order of things has its foundation not only or indeed mainly in all the fertile discoveries in the natural sciences but in the growing knowledge of psychiatry, psychology, the humanities, and religion. Although new understanding and discovery merely push back the curtain of ignorance and never hope to eliminate it, we now have a coherent and reasonably comprehensible picture of the physical world in which we live, even if the ultimate nature of energy and matter defy human comprehension. No doubt they always will. Medical and biological sciences have provided us with a fair view of how the mammalian organism manages its activities, governed by a nervous system which at the end frays out into minute chemical and electrical processes; the ancient humors, hormones, and vitamins, controlling the destiny of cell, organ, individual, and society; methods for keeping microbial invaders and virus enemies at bay with chemotherapy and antibiotics; and our own private internal ocean resembling the sea, our common ancestor in which all life began. These and many other discoveries have given us a reasonable operational picture of the marvelous wisdom of the body and the infinitely complicated simultaneous business of thousands of metabolic mills doing harmoniously their complex and intermingled works.

Not only the body of man but his intricate genetic mechanisms, the unfolding of the Mendelian laws of heredity, the measurement or approximations of intelligence, body type, diathesis, the functions of the conscious mind and of the unconscious, the chemical basis for the stuff of heredity, the behavior of the herd, the intricacies of highly developed societies of ants, wasps, bees, and birds, all give clues as to the organization of man's mind and some of the evolutionary pathways taken by plastic living material. Then we have our own new readings of history which must be reinterpreted by our generation in the light of its own views and problems, the culmination of physical exploration with the conquering of the Antartic and the ascent of Everest, man-made satellites, and the implications of space, new discoveries of ultimate space, with its infinitude of stars, suns, and galaxies, all these give a view of noble promise. While progress has gone on apace in these and many other areas, we have the shocking evils of two world wars with their dehumanizing effects, the communist purges and the Nazi experiments in mechanized extermination of their fellow man. They disclose the fact reiterated so many times, that man has hardly begun to study himself. As he begins to realize the magnitude of the starkest problem before him, the scandalous erosion and leeching of irreplaceable natural resources for energy he is spawning his replicates with the casual accuracy of the sex-obsessed lemming. This becomes catastrophic at a time when medical science has doubled the average duration of human life and removed many of the hitherto effective breaks on overpopulation. As Huxley says, resources are limited, and population must be limited if man is not to turn into a cancer of the planet.

For the biologist and for the scientist today, as well as for the layman, Huxley's book is a beacon. He looks beyond what man has done into a transcendental state which he calls transhumanism, where true and unrealized potentials are reached. The redefinition of man's progress suggests that any evolution in the future will have to be intellectual and spiritual, that there is some evidence that man's physique may be declining already. The unitarian nature of the whole reality of the cosmos, the fact that nature is process rather than static mechanism and the fact that evolution, being directional, provides some of its own energy and stimulus for better organization of mental activity led Huxley to the belief that human destiny will be one of fulfillment. It will bring satisfaction only through a full realization of man's potential. He emphasizes the thought that man's future growth will be cultural rather than strictly biological though it must exist in its biological matrix. The new wine for the new bottles must come from those who recognize that the splendid scientific advances through specialization have left each field cut off from any central core of knowledge. This has produced a monstrous cross sterilization of thought rather than cross fertilization. Man rather than society or the state rises in this concept as the important unit, though the social organism is clearly recognized as an important and growing force. Huxley believes that a new religion will have to arise to satisfy man's eternal yearnings of the spirit. Just how this is to come about, this deeply thoughtful and moving book cannot tell us. Huxley's book, holding a promise for the future, should be an inspiration to anyone who takes the trouble to read it.

Those who have watched the world's leaders fail to evade the holocaust of two world wars have reason to doubt their capacity to deal with the urgent problems of a world in which science is the dominant force. Lawyers, engineers, generals, teachers, as well as a motley array of mobsters and murderers, have not led their several countries along the road of peace. Conflicting ideologies must find prophets to resolve their differences lest disaster put a halt to all such squabbles in a final explosion of unleashed forces. Huxley's book suggests, but does not state explicity, that for survival first and for progress later the leaders of our age must be groundedly learned in science, in politics, in economy, in humanism, and in religion to be wise enough to lead us to salvation. Of these qualities not the least is science, but none can be omitted.

WILLIAM B. BEAN, M.D.

Fundamentals of Electrocardiography and Vectorcardiography. By Lawrence E. Lamb, M.D. Price, $9.50. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

This book is intended to acquaint the beginner with fundamentals of the vector concept as well as electrocardiography and vectorcardiography. The ideas are presented in the usual fashion, but especially from the point of view of the author. There are some aspects of the vector concept, however, which are worthy of note since they do lead to some confusion, particularly for the beginner who may not have sufficient background to realize their significance. Some of these are presented to caution readers of the book.

Answers to the questions "What is a vector?" "What is a point of origin?" "What is an instantaneous vector?" "What is a resultant vector?" "What is a coordinate?" are poorly and vaguely presented. The statement, "There is no force at any point of the plane perpendicular to a vector" is not a correct statement. Apparently, the author wishes to state that if a vector is perpendicular to a plane, no component of the force lies in the plane. Again the statement is made, "It is important to realize that the diagonal of a parallelogram is not equivalent to the magnitude of the actual vectors." The reasons for that statement are not clear. Furthermore, why is the statement made "Electrocardiographic leads are coordinate graphs in counterdistinction to vectorcardiograms which are polygons?" Another statement difficult to understand also is, "Once the magnitude of a force is known, it can be converted into units of time by multiplying its magnitude by its duration of action." Again the author states, "Any particle containing electrical energy is a charged particle." This, likewise, is not clear.

Consider the statement "an effective electric force or resultant force is created when two charged particles of different potential values are close enough to each other for over-lapping of their electric fields. . . . The magnitude is equal to the difference in potential between the two particles." Suppose we do consider two electrons; they set up the same electric fields. Would the author say that the two electrons do not set up a potential field? The author also speaks of forces as being emitted from each charged particle. The word emission may be a little confusing, since it may be considered in terms of radioactive emission. On page 30, under the Fundamentals of Electrocardiographic Instruments, the second paragraph begins with the heading "string gauge galvanometer." It is not clear as to what a string gauge galvanometer is. He may be confusing this with a strain gauge. He speaks of the string gauge galvanometer throughout Chapter 5. This would be confusing to any reader. The statement on page 31, "The string properly adjusted offers little impedance to displacement and as a consequence there is little lag" is difficult to agree with. It depends on performance of various string galvanometers.

On the same page, the statement is made, "For standardization, one millimeter is applied to the conductor." The author surely means one millivolt and not one millimeter.

The author states, "These spatial loops are polygons." The statement of polygons used in this sense is not geometrically correct.

The electrocardiograms which are presented in the illustrations have been very poorly touched up. Most of the recordings appear to have been obtained with a direct writer and relatively poor recorder which necessitated touching up in many instances.

It would appear, therefore, from these few comments that the book is very poorly and loosely written. The book is of no special value and it is unlikely that it adds anything really significant to medical literature.

G. E. BURCH, M.D.

Clinical Enzymology. By Gustav J. Martin, Sc.D. Price, $6. Pp. 241, with 9 illustrations. Little, Brown & Company, 34 Beacon St., Boston, 1958.

The volume reviews the information at present available about enzymes used clinically, including trypsin, chymotrypsin, streptokinase, ribonuclease, deoxyribonuclease, hyaluronidase, and cholinesterase. The text covers the chemistry of enzyme action, the parenteral use of enzymes (not topical application), and the diagnostic use of enzymes, such as amylase, phosphatases, and others. Trypsin receives major emphasis in the text. It is regrettable that critical analysis of some of the clinical results with enzymes is not included. The volume, however, is interesting. It offers the reader considerable information regarding enzymes used in clinical medicine not at present available in any other single volume with which the reviewer is acquainted.

S. E. Ziffren, M.D.

A Textbook of Clinical Neurology, Eighth edition. By Israel S. Wechsler, M.D. Price, $11. Pp. 782, with 179 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

Today, the medical student is faced with a choice of new books that have further parcelled the already parcellated books in the separate specialties. Now, in neurology, many of the new tests either deal with the clinical examination or the disease entities. This is fine for book publishers, but not for the student. The eighth edition of Wechsler's combines both, along with a supererogation of fine chapters on the neuroses and history of neurology. It is refreshing that it is an intimate book in which the personal views of a consumate observer are expressed. The author is not afraid to use, "I believe" (apparently the first person singular is anathema in current textbooks and scientific writing), and he intersperses the descriptive matter with his thoughts on a variety of controversial subjects in the field. It provides a change for the reader who is currently faced with compendiums written by a galaxy of experts who present their subjects as innumerable references so that we do not know what they themselves think, if they have thought at all.

The book's major defect is the lack of material about current advances in the pathophysiology, chemical changes, and treatment of certain diseases. A few examples are the presentation of isochromism of nerve and muscle which has been severely dealt with by the English neurophysiologists, accusing the loaded rectum as a cause of sciatica (a musty Gowersism), and not mentioning the role of ceruloneplasmin in Wilson's disease. This detracts from its otherwise fine portions on description and diagnosis. It is beautifully illustrated, and the printing and format are excellent. The book may be recommended to students and residents with the reservations noted above.

R. J. Joynt, M.D.

The Century of the Surgeon. By Jurgen Thorwald. Price, $5.95. Pp. 432, with 66 illustrations. Pantheon Books, Inc., 333 6th Ave., New York 14, 1957.

Allbutt once wrote a very searching essay on the historical relations of medicine and surgery. Sensible physicians agree that these relations should be close and warm. Thus, we welcome a work which tells the story of medical advances of the last hundred years from the surgeons vantage point. In this scholarly and delightful book, Jurgen Thorwald has made a story of surgical progress in the last hundred years, using the device of a narrator in the first person as an eyewitness of many notable events. The narrator tells of being an undergraduate medical student, a practicing surgeon, or a retired medical dilettante as the story requires. Though the book has the autobiographical impact of a story in the first person, it is based upon painstaking and scholarly research. The documentation is that of a scientific treatise or a genuine biography. The story begins with the author an undergraduate student at Harvard in 1843. Despite the advances of the anatomists and pathologists, surgery still lingered in the long night of pain and pus, surgical slashing to set speed records, technical skill, hemorrhage, trauma, and mortality rates which often approached the neat perfection of one hundred per cent. John Collins Warren is an example of the necessary ferocity of the surgical approach in the days before anesthesia.

Then there is a fascinating aside on the ancient and recent history of bladder stones, the remarkable cures done in India and France one hundred to two hundred years ago. Another digression deals with the rise of plastic surgery in India and the Orient, where a woman's

nose might be amputated by a husband suspecting infidelity; or a conquering general might unnose an entire population.

The great dawn of the emerging "century of surgery" has the oft told but always interesting story of anesthesia; its memorable human struggles between greed and altruism; and the sharp initial incredulity giving way to a remarkably rapid general acceptance. This discovery at once made surgery leap forward in exuberance with new operations. Soon it ran aground on the hideous reality of pandemic infection, especially in hospitals and battlefields. The role played by various historical characters is given with photographic fidelity, although Crawford Long is disposed of in a casual aside which may have Hugh Young in torment as he turns over in his grave. The mass of horrors and the extent of human misery are emphasized. The role of dirt and germs in infection was not recognized. Into this holocaust of surgical havoc, almost universal infection was robbing surgery of the boon of anesthesia. The utility of scrupulous cleanness was proof of the validity of antisepsis and later asepsis. Lister, Pasteur, and the hostile contemporaries against whom they had to wage stubborn battle are presented as devoted knights with high mission, courage worthy of their vigorous opponents. Semmelweis and his destruction by the pontifical professors who denied even the possibility that they might be wrong are illustrated with fidelity and power. We have marshalled in parade before us men whose names are etched deep in the monuments of medical history. Other less known or casual actors on the scene have their part here or there.

This book is surprisingly successful in its effort to reach romance through realism. It approaches medical history as a historical novelist would, using the form of an autobiography. The only place where this mechanism seemed forced was in the author's discussion of his failure to recognize by symptom or by sign the carcinoma of the stomach which was to kill his wife just at the time when operations for this disorder were beginning to save lives. Altogether, this is an interesting and very well written book which should appeal not only to surgeons, who may rather easily see themselves as heroes, but also to internists and general physicians, as well as anyone interested in the truly superb advances of scientific and humane medicine during the last hundred years.

WILLIAM B. BEAN, M.D.

A Classified Bibliography of Gerontology and Geriatrics: Supplement 1, 1949-1955. By Nathan W. Shock. Price, $15. Pp. 525, with illustrations. Stanford University Press, Stanford, Calif., 1957.

The burgeoning interest in aging, reflecting perhaps the self-conscious attention to itself of an aging population, is illustrated in the fact that this supplement which Nathan Shock has prepared of the publications from the past six years, contains about as many entries as a similar bibliography of similar publications for the first half of the present century. The Forest Park Foundation of Peoria, Ill., has made possible the great volume of work which has led to the publication of this book. It will be greeted enthusiastically by anyone working in the field of gerontology and by anyone else who needs to look up a particular topic or aspect of the problem. The arrangement of the book facilitates ready reference and in addition there is an alphabetical list of authors. For all of us who are getting old, it may or may not be some comfort to know that there are now seventeen journals devoted to the problems of aging. Within the span of years covered by the book almost sixteen thousand articles were published on different aspects of aging. This will be an indispensible reference book for those working in the field and will be a great help to anyone who has a related problem upon which he needs to get at the available publications.

WILLIAM B. BEAN, M.D.

Drugs: Their Nature, Action and Use. By Harry Beckman, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry; Consulting Physician, County General Hospital and Columbia Hospital. Price, $15. Pp. 744, with 126 figures and many structural formulae. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

Textbooks on pharmacology have assumed increasing importance in the education of the physician. Acceleration in the discovery of new drugs of high potency and specificity has become so great that more than ever before the mastery of the facts and methods of pharmacology is a necessity for the student and practitioner. Approximately one-third of the national cost of medical care is now attributed to the purchase of drugs. There is no question that this amount is excessive and some of the blame can be directed at the physician who is unduly

influenced by multimillion-dollar advertising campaigns and practices of polypharmacy. The deluge of misleading advertisements which clutter the doctor's mail demands increasing discrimination by physicians who are thoroughly grounded in the science of pharmacology. The principles of this science must be inculcated in the medical schools to a greater extent than has been the case during the last thirty years.

The author's preface states that the present book is intended for undergraduate medical students. The first fifty-eight pages contain an admirable discussion of the subject of pharmacology which should give the reader a clear insight into the problems of evaluating drugs and searching for new ones. The remainder of the text is devoted to discussions of individual therapeutic agents, grouped conveniently and logically, with emphasis on their fundamental actions rather than their chemical composition. For example, there are separate chapters entitled "Drugs that Stimulate Uterine Muscle"; "Drugs that Depress Uterine Muscle"; "Drugs that Stimulate Cardiac Muscle"; "Drugs that Depress Cardiac Muscle." In the presentation of material on individual drugs the author gives both the pharmacopeial and the chief proprietary names. Subheads include "Source, Nature, and Preparations"; "Clinical Effects"; " Nature of Action"; "Absorption, Distribution, Metabolism and Excretion"; "Dosage"; "Side-Actions, Toxicity, and Contraindications."

The author's literary style is personal, engaging, and generally effective. It is rather a relief from the conventional, dry, impersonal writing to which most medical authors are addicted. The presentation is much aided by the publisher, who has used good typography and nonglaring paper. The total result is a very readable book.

This reviewer would have liked to see included in the first part critical discussions of how new drugs are tested clinically before acceptance for use by the Food and Drugs administration; of the difficulties in enforcing the present laws against misleading advertising; of the cost of drugs to the patient; of the selection of proprietary names for new drugs; and such other subjects as would equip the physician to deal with the techniques of Madison Avenue which the pharmaceutical houses have adopted.

In the discussion of individual drugs the emphasis of space allotted has been given to the clinical use with frequently a paucity of detail concerning the pharmacologic aspects. The prevailing opinion about drug action is stated with little evidence for or against such a view. The clinical use of the drugs is often based on one paper, whereas many others are also available and their citation would tend to assure the reader of the authenticity of the views expressed. The brilliant contributions of pharmacology to the treatment of diseases of the thyroid gland are dealt with in disappointing brevity. For example, the physiologic facts of sodium liothyronine (sodium *l*-triiodonthyronine) are presented in eighty-three words; this seems to me to be inadequate. In general, the author seems to have tried to compress the very large subject of pharmacology into too small a space. I believe that the student would get an inadequate insight into the science without supplementation with extensive lectures and demonstrations.

ELMER L. DEGOWIN, M.D.

Nierenkrankheiten: Physiologie, Pathophysiologie, Klinik and Therapie. By Hans Sarre, Dr. Med. Price, $14.05. Pp. 540, with 118 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart, N, 1958.

The reviewer apologizes for the delay in preparing this review. Unfortunately, he does not read German fluently. Originally he thought he could skim through the table of contents, read several sections, and make the comment that this book is similar to Fishberg's "Hypertension and Nephritis" and entirely suitable as a substitute for anyone who reads German efficiently. However, reading a few sections was a sufficient stimulus for a number of evenings spent with German-English dictionaries in laborious translation. Although much of the ground covered is familiar territory (but well done and well illustrated), the effort was rewarding. The author has a facility not only for thoroughness, but also for presenting the essentials of a subject briefly and clearly. The ground covered is extensive and I recommend this book to the serious student of renal disease who wishes up-to-date, concise, and critical summaries of a variety of diseases. The medical student or beginner in renal disease also should find this a valuable book. Among other things, complete and specific details are given, not only for simple procedures related to the study of kidney disease, but also for clearances, hemodialysis and the like. I can find a few faults, such as references given in the text but missing from the bibliography, and sometimes reliance is placed on rather one-sided or secondary sources of information (as in the case of Epidemic Hemorrhagic Fever).

The entire volume is elegant—fine paper and printing, intelligently chosen illustrations, and extremely valuable to me (at least) an attached ribbon page marker. I wish that an English translation were available.

DAVID P. EARLE

The Psychology of Medical Practice. By Marc H. Hollender. Price, $6.50. Pp. 276. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

This book was written to aid physicians in handling psychological problems commonly met in medical practice. Following a discussion of the doctor-patient relationship, common problems in the fields of medicine, surgery, obstetrics, and pediatrics are considered. A separate chapter deals with the problems presented by the patient with cancer and a concluding chapter considers the pros and cons of nonmedicinal prescriptions, such as vacations. The book is written as a series of questions and answers: What should you tell a patient about his illness? How should you tell a patient about his illness? What does a heart attack mean to the patient? How do you prepare a patient for long-term rehabilitation? How should the patient with cancer be prepared for surgery? How should you approach a patient if her baby is a monster? What should the physician's attitude be about using a placebo? These and many similar practical questions are posed and answered. The author, however, expressly states that it was not his intention "to provide cookbook-like recipes" but "rather to evolve general principles and to illustrate an approach." The basic principle emphasized throughout this book is that the reactions of the patient to his illness, to his doctor, and to the treatment prescribed must be thoughtfully considered if the physician is to practice medicine as an art rather than as a trade. Written in simple, nontechnical language, this book should be of value and interest to those for whom it was written—physicians wishing to handle the psychological problems of everyday practice.

W. W. SCHOTTSTAEDT, M.D.

Unexpected Reactions to Modern Therapeutics: Antibiotics. By Leo Schindel, M.D. Price, $3. Pp. 146, with 10 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

The title of this book is attractive. It is, therefore, disappointing that the contents fail to live up to this initial promise. Much of the text reports this and that regarding antibiotics, and little of it weighs and assesses these reports. If an author writes a book from filing cards it is best that he disguises the fact by careful editing. In eleven successive paragraphs, starting on page 129, Dr. Schindel begins nine of them with the equivalent of "John Doe et al. have reported. . .gave. . .also reported. . .treated. . .mention etc." The English is difficult to read in many places and in some it is quite wrong, namely: sporiferous, subfebrile, sensibilization, and per oral. In three cases, work by authors mentioned in the text is not listed in the bibliography, and there are at least eleven misprints. There appears to be a direct contradiction between statements made regarding drug rashes on pages 119 and 125. A lot of interesting facts are hidden away in this book if you wish to delve for them.

The book is not recommended.

IAN MACLEAN SMITH

Therapeutic Exercise. By Sidney Licht, M.D., with 36 contributors. Price, $16. Pp. 893, with 204 illustrations. Elizabeth Licht, Publisher, 360 Fountain St., New Haven, Conn., 1958.

Dr. Sidney Licht, Assistant Clinical Professor of Medicine, Yale University School of Medicine, is one of the leading experts in rehabilitation in the United States. He has now edited a volume of 893 pages on "Therapeutic Exercise," compiled by thirty-six physicians. Dr. Licht himself has contributed three papers, one on "Kinetic Occupational Therapy," one on "History," and an appendix on exercises in general. They all reflect his great learning and experience. Of special value are also the accounts by Dr. Christian Coers, of the University of Brussels, on "The Motor Unit," by Professor H. W. Knipping and Dr. H. Valentin of Cologne University, on "Sports in Medicine," and by Dr. Arthur S. Abramson, of Yeshiva University, New York, on "Exercise in Paraplegia." Other sections are less satisfactory. A chapter which should not have been included is that of Wilfred Barlow, on "Posture and Its Re-Education."

There are chapters on "Exercise in Orthopedics," side by side with others on "Exercises for Scoliosis," "Exercises for Hemiplegia," and "Exercises for Cerebral Palsy." The overlapping reflects the dilemma in which physical medicine in the United States finds itself at present. Rehabilitation insofar as it relies on exercise does not allow a categorization of the subject in

diagnostic entities. The assumption implied by the above arrangement, viz. that a certain type or sequence of exercises is indicated for certain nosological categories, like digitalis for myocardial failure, or penicillin for acute gonorrhea, simply is not correct. Dr. Licht is no doubt aware of this dilemma, though it is perhaps only after completing a vast study such as this that the axiomatic differences between the theoretical bases of "Therapeutic Exercise" and of clinical medicine become apparent. Exercise therapy is characterized by a unique element of nonspecificity, very much in contrast to other sections of clinical therapy; while it has emphasized the importance of new diagnostic features which formerly were not always considered of crucial importance; for example those pertaining to the "stability" as against "activity," of certain pathological processes which frequently call for rehabilitative evaluation, e. g., in coronary occlusion, atherogenesis, diabetes, the various forms of systemic arthritis, or in the degenerative diseases of the nervous system.

To have produced an exhaustive technical work on present-day practices of exercise therapy is an achievement of which Dr. Licht can justly be proud. More than any other discipline of clinical medicine the subject is in midstream. In ten years from now it will present a very different appearance. New conceptual and didactic components, some of them taken from European "Versehrtensport"; from modern systems of educational gymnastics in Scandinavia, or from social games practiced in this country—to name only a few—will supersede numerous activities and techniques currently practiced in American rehabilitation centers. Many of them will then appear to be fossilized rituals from a semimythological past to which only historical interest is due. Dr. Licht's volume will at that stage render it possible to evaluate the significance of such advances in therapeutic exercises as are bound to take place in the near future.

ERNST JOKL, M.D.

Fundamentals of Neurology. Third edition. By Ernest Gardner, M.D., Professor of Anatomy, Wayne State University College of Medicine, Detroit. Price, $4.75. Pp. 368, with 210 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

The preface to the first edition of this book states that it is addressed to students in such varied disciplines as nursing, biology, psychology, physical therapy, and occupational therapy. With this end in view, the book is written along simple and basic lines. As a simple and preliminary survey of neuroanatomy and neurophysiology, the author succeeds admirably. The illustrations are excellent and the style is lucid. Each chapter has at its end an excellent critical listing of pertinent references. As well, in each chapter, there are brief and informative notes on some famous investigators and clinicians who have influenced neurology.

The book may be recommended as introductory reading to the freshman medical student, though its lack of detail would be a drawback in a medical curriculum.

DAVID GREEN, M.B., B.S. (MELB).

Ciba Foundation Symposium on Bone Structure and Metabolism. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. and Cecilia M. O'Connor, B.Sc. Price, $8. Pp. 299, with 121 illustrations. Little, Brown & Company, 34 Beacon St., Boston, 1956.

The book presents a series of talks by scientists actively engaged in research on various aspects of bone structure and metabolism. Since these papers represent the core of a symposium under the auspices of the Ciba Foundation on bone structure and metabolism, the discussion which follows each presentation is a vital and stimulating part of the book. The numerous illustrations are of excellent quality on glossy paper. The topics covered include the structure of bone from the anatomical to the molecular level; structure of bone salts; the histological remodeling of adult bone by autoradiographic study; fibrogenesis and the formation of matrix in developing bone; the mucopolysaccharides of bone; autoradiographic studies of the formation of the organic matrix of cartilage, bone and the tissues of teeth; uptake of radioactive sulfur in the differentiation and growth of cartilage and bone; in vitro uptake and exchange of bone citrate; magnesium content of bone in hypomagnesemic disorders of livestock; the mechanism of nutrition in bone and how it affects its structure, repair, and fate on transplantation; studies on the repair of fractures using radioactive phosphorus; metabolic studies on vitamin D; the mode of action of vitamin D; variations in sensitivity to vitamin D—from vitamin D—resistant rickets, vitamin D-avitaminotic rickets, and hypervitaminosis D to idiopathic hypercalcemia.

Topics which would be of more direct interest to internists include present knowledge of parathyroid function, with especial emphasis upon its limitations, the indirect assessment of parathyroid function, vascularity of bone in relation to pathological studies, some observations on experimental bone disease and bone as a critical organ for the deposition of radioactive materials.

Each of these articles has a short but key bibliography. It is the type of book which would give internists and others not in the field of bone research a better understanding of the complex nature of bone structure, its repair, and the many metabolic and physiologic reactions which take place.

MICHAEL BONFIGLIO, M.D.

Negroes and Medicine. By Dietrick C. Reitzes. Price, $7. Pp. 400, with appendices. Harvard University Press, 79 Garden St., Cambridge 38, Mass., 1958.

The study reported in this volume was conducted at the sociology department of the University of Chicago through funds provided by the Rockefeller Foundation. The supervising committee included Prof. Everett C. Hughes and Prof. Philip Houser, of the department of sociology, and Prof. Franklin C. McLean, of the department of physiology, with the author directing the study, which extended from Oct. 1, 1955, through March 31, 1957. The first section of the report presents a statistical analysis of certain facets of medical education for Negroes. Data dealing with this analysis of Negro students and applicants were obtained from the Association of American Medical Colleges, the registrars of Howard University School of Medicine and Meharry Medical College and a questionnaire survey of the other approved medical schools in the United States. Statistical information indicates that between 1938-1939 and 1955-1956 the number of Negro medical students in the United States increased 117% (from 350 to 761), while all medical students increased 34.4% (from 21,302 to 28,639). The proportions of Negro students attending medical schools other than Howard and Meharry has gradually increased from 12.9% in 1938-1939 to 31.0% in 1955-1956. This section of the report presents a comprehensive portrayal of the problems encountered by Negro students in premedical preparation, the M. C. A. T. scores of Negro students, the relation between type of college and type of medical school, regional patterns and scores of Negroes in predominately white schools, as well as other material of interest and educational importance.

The second section of this report presents an interesting analysis of medical care by and for Negroes, resulting from a study of fourteen communities—Philadelphia; New York; Boston; Chicago; Gary; Detroit; Indianapolis; Los Angeles; Washington, D. C.; St. Louis; Kansas City, Mo.; Atlanta; New Orleans, and Nashville, Tenn. The communities range from "no integration" to "high integration" and in each instance local sociologists supplied background data for the community, local human relations organizations were consulted, and selected lists of persons were interviewed. This section of the volume is fascinating and informative reading, as it reveals the problems encountered by Negro physicians and patients in various parts of the nation. The final summary dealing with patterns of medical care presents some important data and questions evolving around the factors affecting integration patterns. Appendices include medical-education tables, the medical-college-admission test, and medical-care tables.

This volume appears to be a valuable contribution to the field of race relations. It presents problems of particular importance to medical education and to medical care and merits careful study by all those interested and concerned with these fields of endeavor.

EDWARD L. TURNER, M.D.

A Doctor Speaks His Mind. By Roger I. Lee, M.D. Price, $3. Pp. 120. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

Those who chuckled over Roger Lee's outspoken autobiography, "The Happy Life of a Happy Doctor," will enjoy this group of essays called "A Doctor Speaks His Mind," by a man who has been an important figure in American medicine, medical education, and practice. Some of the views expressed in this bundle of essays were suggested, and a few were developed in his autobiography. Not only for medical educators and investigators, but for those who are practicing, his discussions of our current and future problems bring the fresh, personal views of a thoughtful physician. They are useful and most welcome, despite the fact that many will disagree with some of them. I was particularly pleased with his essay on hero worship. Many others give a current comment by one who has had much experience with his fellowman.

It may seem a little rude to suggest to a Harvard physician that somebody had better check his references and his quotations. For instance, on page 89 he attributes to William Harvey the complaint about his angina pectoris—"I am at the mercy of any rascal who chooses to annoy me" which is John Hunter's classical commentary on committees and administrators. On page 111, Bruce, of London, is famous for his work on brucellosis and sleeping sickness, not for any substantial contribution to malaria. Finally, there is a sentence which may cause a certain amount of quivering of the muscles, weakness of the limbs, and sludging of the blood in the present-day endocrinological Brahmins of Boston; it follows: "There is a substance generally known as cortisone, which is a mixture of pituitary, renal, and perhaps other glandular substances." In addition to puckering the foreheads of proper Bostonians, this will probably displace a certain amount of air by raising the collective eyebrows of the Mayo Clinic. But these scars of carelessness do not seriously deface these chatty and thought provoking essays.

WILLIAM B. BEAN, M.D.

Florence Nightingale and the Doctors. By Zachary Cope, M.D. Price, $5. Pp. 163. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5, 1958.

Much has been made of the enigma of Florence Nightingale. From Cope's most illuminating study of her very important relations with doctors she emerges as a tense, high-strung, frustrated, mother-dominated woman who finally broke away. Then she was able to devote her life singlemindedly to what she considered her God-given mission, that of establishing nursing as a respectable profession. Her "illness' she used skillfully, perhaps unconsciously, but I believe with subtle insight in order to gain many of her designs. The medical world and the important political figures came to her door, though one person at a time and never more than a few on any one day. They danced to her tune, coming and going to do her missions, to enhance her position of authority, to take advice and help fulfill her high aims.

Florence Nightingale, more than most, was a woman of paradoxes. While reading Cope's fascinating book, my opinion would waiver from that of enthusiastic pleasure to disgust. She was not in favor of teaching nurses too much pure medicine "for she thought it would make them either intolerable from airing their knowledge or miserable presumably from seeing methods adopted which were not in keeping with the methods they had been taught were the best." She was against all certificates, boards, and degrees, preferring to set high standards and reach her objectives by discipline and training. On the other side, Cope brings out clear evidence that it was her custom to ask for information, not to ascertain the truth of a doubtful question but to "enable her to be provided with arguments which she could use to support already definitely held convictions." Though Cope believes she did not use her invalidity willfully, it served her purpose in every way by giving her the time to attend wholeheartedly to her mission, to gain the concentrated leisure for consecrated attention, to avoid frivolity and society thus gaining time for extensive reading, writing, and thinking. She was interrupted only as she chose to be.

One wonders what might have been her fate and the progress of the nursing profession had she been flushed from her lair by a more vigorous romantic assault by Moncton Milnes. Would she, like Elizabeth Barrett, have forsaken the bed of neurotic invalidism for the nuptial couch, or would it all have ended disastrously? Perhaps it was Florence Nightingale's fabulous power of bending men to her will by some mysterious but all pervasive attraction which enabled her to accomplish her mission in that very masculine Victorian world when the average man had as his prime rubric the notion that whatever women might be they were devoid of intellect. Correct deportment and gentlemen's maneuvers left the men she encountered and outwitted without any effective weapon of counterattack. Thus in the grip of her powerful neurosis, she was able to use techniques of mastery with little regard for facts or evidence to accomplish her end. She was a woman of powerful intelligence and high motivation. The world is fortunate that her ambition and her purpose were so constructive and humane for she bullied and browbeat the helpless men and if necessary coerced with methods approaching gentle blackmail.

As one reads Cope's charming discourse and sees paraded before us the gallery of physicians with whom Florence Nightingale dealt, observes her ruthless but effective tactics, one must admire the fiery determination which enabled this "frail" woman to be supported and borne up by the neurosis which served her purpose so exquisitely. I wonder how much she really understood of her own feelings. Reading her "Notes on Nursing" must make us admire her keen intellect and her accomplishments against high odds. Cope's book, however, brought to my eyes a tear of pity for the pompous and bewildered Victorian gentlemen whom she led about

gracefully but willfully by their side whiskers in a state of perpetual and bewildering one-upmanship.

Florence Nightingale chose a noble mission which she believed was directly inspired by God, accomplished her high purposes in the face of improbable odds, using her intellect, her femininity, and her neurosis with telling effect. Physicians who may be fretful about the nursing profession, as nurses aspire to the role of physician and leave nursing for aides and practical nurses, should remember the fate of physicians who opposed such women as Florence Nightingale.

WILLIAM B. BEAN, M.D.

The Esophagus: Medical and Surgical Management. By Edward B. Benedict, M.D. and George L. Nardi, M. D. Price, not given. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

The extensive experience of two men interested primarily in the endoscopic and surgical approaches to the esophagus is related in a clear, uncomplicated fashion in this well-printed volume. Emphasis is placed on detailed descriptions of various diagnostic and therapeutic maneuvers: the use of the rigid esophagoscope; the techniques, advantages, and hazards of bouginage; and operative procedures are thoroughly covered. Physiology is not stressed, and medical management is only sketchily presented, detracting from the over-all value of the book. The anatomical pictures, taken from a Ciba publication, are clear, but many of the x-ray reproductions are hazy and the abnormal findings not well delineated. The book will be particularly useful to those interested in the manipulative aspects of the diagnosis and treatment of esophageal disorders.

BERTRAM FLESHLER, M.D.,
and
FRANZ J. INGELFINGER, M.D.

The Liver and Its Reactions in Africa. Published in *The Leech*, Vol. 27, No. 2, 3, and 4 (Feb.-April) 1958. Edited by B. Kaminer M.B.B.Ch. (Rand), D.C.H. (Eng.). Dr. P. V. Tobias, editor of "The Leech." Price, not given. Pp. 131. Medical Graduates Association & Students Medical Council, University of the Witwatersrand, Johannesburg, 1958.

This monograph contains the papers presented at the Fourteenth Annual Conference on African Medicine, held in Johannesburg in May, 1958. It is particularly concerned with the special aspects of liver disease seen in the native populations.

Various authors discuss the influence of malnutrition in early life on the metabolism of the liver and its role in increasing the incidence and severity of later hepatic disease. Several authors deal with primary tumors of the liver, pointing out their frequency of occurrence and fulminating course in Africans as compared to Americans and Europeans. The problem of parasitic infections, especially schistosomiasis and amebiasis as they affect the liver is also considered.

Unfortunately, there is some repetition and only a few of the papers present new approaches or are concerned with clinical or laboratory investigations. Particularly interesting are papers dealing with "Steroid Hormone Metabolism in Liver Disease," and "Alterations in Carbohydrate Metabolism Associated with Neoplasia."

This publication should be of value to physicians dealing with hepatic disease or tropical medicine; however, it will have limited interest for most readers of the ARCHIVES.

J. R. WEBSTER JR., M.D.

Correlative Neuroanatomy and Functional Neurology. By Joseph G. Chusid and Joseph J. McDonald. Price, $4.50. Pp. 345, with 220 illustrations. Lange Medical Publications, Los Altos, Calif., 1958.

This is a revision of a popular book dealing with correlative neuronanatomy and functional neurology. It is directed to the beginner in neurology and is intended as an aid or supplement to standard neurological texts and literature. In this respect the authors have done an admirable job. This book is remarkably thorough in its coverage of important details. The illustrations are excellent. An abundant number of charts is included. Because of the emphasis upon anatomy, the clinical descriptions of diseases of the nervous system are necessarily brief. This book is highly recommended to the resident in neurology and others who are interested primarily in morphology of the nervous system.

A. L. SAHS, M.D.

Etiology and Treatment of Leukemia. Edited by Walter J. Burdette. Price, $4. Pp. 167, with 10 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1958.

In this small volume of 167 pages are the papers which were presented at the Cancer Conference of the Louisiana Division of the American Cancer Society, together with the discussion and the questions raised after each presentation. The book has two main themes. The first is on the etiology and diagnosis of leukemia and the second portion on the treatment of leukemia. There are twelve papers, all of which are short presentations consisting essentially of a discussion of the current concepts or a summary of one phase of the problem. These are brief, concise, and informative, without minute details. Each paper is followed by a record of the spontaneous discussion and questions raised by other participants in the program. The papers are authoritative and up to date.

The subjects covered are I. Viruses and Cancer (Jerome T. Syverton); II. Etiology of Leukemia (Arthur Kirschbaum); III. Infectious Concepts of Leukemia (Ludwik Gross); IV. Filterable Agents Prepared from Leukemic Tissue Causing Leukemia and Other Cancers in Mice (George W. Woolley); V. Factors Influencing Induction of Myeloid Leukemia in RF Mice by Irradiation (Arthur C. Upton and Jacob Furth); VI. Diagnosis of Leukemia (Charles C. Sprague); VII. Laboratory and Clinical Approaches to Leukemia Chemotherapy (Alfred Gellhorn); VIII. Irradiation Therapy of Leukemia (Joseph V. Schlosser); IX. The Use of Chlorambucil and Busulfan in the Treatment of Leukemia (Morwenna Till); X. Treatment of Leukemia (Joseph H. Burchenal); XI. Clinical Management of Leukemia (William R. Arrowsmith), and XII. Etiology and Therapy of Leukemia (Walter J. Burdette).

There is an extensive bibliography at the end of the book for those desiring more detailed information on the subject. This is an excellent survey and summary of the present concepts of etiology and treatment of leukemia.

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References:

1. Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology 8:504, Dec. 1957.
2. Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.
3. Eskwith, I. S.: The holistic approach to angina pectoris. Am. Heart J. 55:621, April 1958.

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Jordan and Grossman; Arch. Surg. 74: 871, 1957
Shingleton, et al; Surgery, 42: 12, 1957
Longmire, Jordan and Briggs; Ann. Surg. 144: 681, 1956
Krane; Am. Pract. and Digest, 8: 1275, 1957

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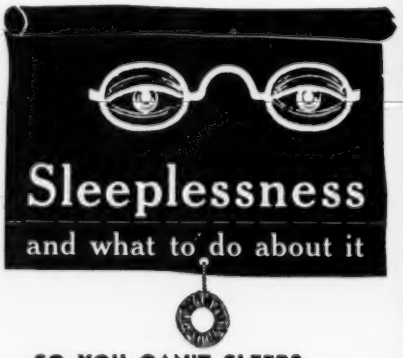

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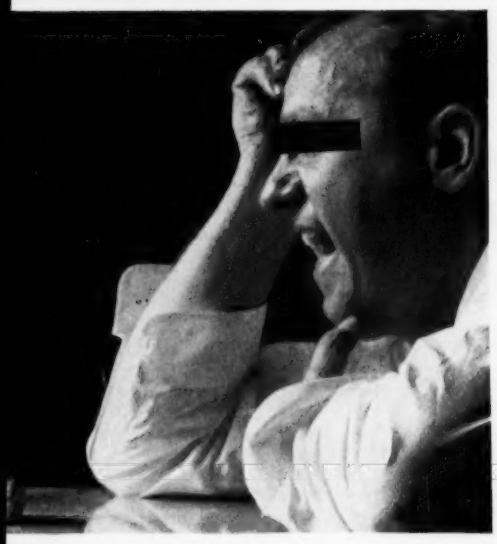

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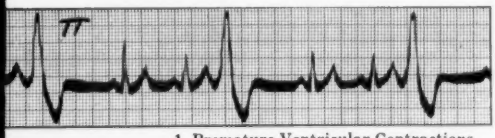

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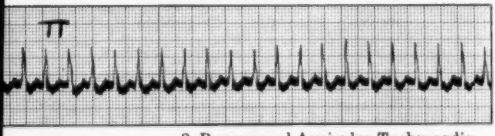

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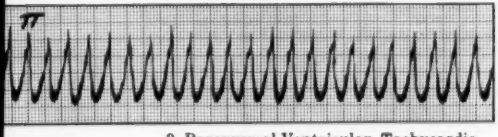

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REFERENCES: 1. Miller, R. F.: Clinical Review, Vol. 1, No. 2 (July) 1958. 2. Van Gasse, J. J.: Clinical Medicine, 5:177-181 (Feb.) 1958. 3. Burrell, Z. L., et al.: Am. J. Cardiol., 1:624 (May) 1958. 4. Hutcheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 118:451 (Dec.) 1956.

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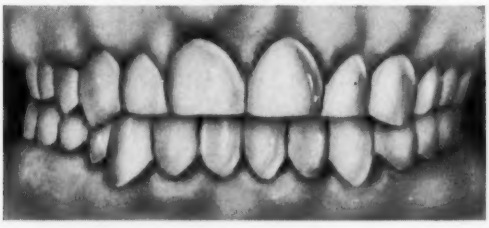

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References: 1. Crunk, G. A.; Naumann, D. E., and Casson, K.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia Inc. 1958, p. 397.
2. Newcomer, V. D.; Wright, E. T., and Sternberg, T. H.: Antibiotics Annual 1954-1955, New York, Medical Encyclopedia Inc., 1955, p. 686.

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